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ORIGINAL ARTICLE

Genetic polymorphism in matrix metalloproteinase-9 and transforming growth factor-β1 and susceptibility to combined pulmonary fibrosis and emphysema in a Chinese population

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Abstract In this study, we aimed to explore the association of genetic polymorphism in matrix metalloproteinase-9 (*MMP-9*) and transforming growth factor-β1 (*TGF-β1*) and the susceptibility to combined pulmonary fibrosis and emphysema (CPFE). We examined the polymorphisms of the *MMP-9* C-1562T and *TGF-β1* T869C in 38 CPFE patients, 50 pulmonary emphysema patients, and 34 idiopathic pulmonary fibrosis (IPF) patients. The frequencies of polymorphic genotypes in *MMP-9* were 78.95% CC and 21.05% CT in CPFE group, 76.0% CC and 24.0% CT in emphysema group, and 100.0% CC in IPF group. There were highly statistically significant increased frequencies of the CT genotype and T allele in CPFE and emphysema groups compared with IPF group ($p < 0.05$). The frequencies of polymorphic genotypes in *TGF-β1* were 2.63% CC, 28.95% CT, 68.42% TT in CPFE group, 4.00% CC, 16.00% CT, 80.00% TT in emphysema group, and 5.88% CC, 41.18% CT, 52.94% TT in IPF group. Significant increases in the TT genotype and T allele frequencies were observed in emphysema group compared with IPF group ($p < 0.05$). Our study has showed that T allele in *MMP-9* (C-1562T) and T allele in *TGF-β1* (T869C) are risk factors of pulmonary emphysema. The T allele in *MMP-9* (C-1562T) possibly predisposes patients with pulmonary fibrosis to develop emphysema.
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Introduction

Pulmonary emphysema and idiopathic pulmonary fibrosis (IPF) are two distinctive diseases with different clinical manifestation, physiology, and pathology. Pulmonary emphysema is characterized by breakdown in alveolar wall, abnormal dilation in the distal end of the terminal bronchiole in pathology, and increases in residual volume and total lung capacity in physiology. IPF is characterized by the accumulation of mesenchymal cells and their connective tissue products within alveolar walls and alveolar air spaces and decrease in the lung capacity. For a long time, they are considered as two independent diseases. However, Wiggins et al [1] reported eight patients with combined cryptogenic fibrosing alveolitis and emphysema in 1990. Since then, similar case reports were reported one after another. In 2005, Cottin et al [2] named this disease as combined pulmonary fibrosis and emphysema (CPFE) for the first time. Subsequently, reports regarding CPFE were increased. However, most studies were retrospective clinical studies. The pathogenesis of CPFE was still unknown. How can two diseases coexist in the same individual? Why do some patients present only emphysema and others present only pulmonary fibrosis? This is still a pending challenge.

To date, although the underlying mechanisms of emphysema and IPF have not been fully understood, a genetic predisposition of emphysema and IPF has been strongly evidenced. The interaction between environmental and genetic factors leads to different phenotypes. Based on these results, the role of genetic factors in the development of CPFE should be considered. There are many candidate genes for emphysema. One such candidate is the group of genes that code for matrix metalloproteinases (MMPs), which play an essential role in tissue remodeling and repair associated with emphysema. MMPs are also implicated in the pathogenesis of pulmonary fibrosis [3—5]. In the early phase of pulmonary fibrosis, MMPs may play an important role in degrading the basement membrane, thereby facilitating the inflammatory cell migration. In the late stage of pulmonary fibrosis, MMPs may play a role in the process of repair [6]. Transforming growth factor-β1 (TGF-β1), the most potent fibrogenic cytokine, is essential in the progression of pulmonary fibrosis. TGF-β is also an important regulator of MMP expression. It inhibits MMP-9 and MMP-12 expression in alveolar macrophages and monocytes [7]. In emphysema, decreased TGF-β signaling may lead to increased MMP expression and subsequent extracellular matrix degradation, which may contribute to existing genetic or acquired susceptibility to emphysema [7]. Otherwise, MMP-9 can activate latent TGF-β to its active form and to induce TGF-β production [8]. Overall, these findings emphasize an important role of the TGF-β-MMP axis in the development of emphysema and pulmonary fibrosis.

The aim of this study was to elucidate the association between *MMP-9* and *TGF-β1* genetic polymorphisms and CPFE among Chinese people.

Methods

Patients

In total, 38 consecutively enrolled patients attending the Department of Respiratory Medicine in Shanghai Sixth People's Hospital were included. CPFE was diagnosed by radiology according to Cottin et al [2]: firstly, the presence of emphysema on high resolution computerized tomography (HRCT), defined as well demarcated areas of decreased attenuation in comparison with contiguous normal lung and marginated by a very thin (<1 mm) wall or no wall, and/or multiple bullae (>1 cm) with upper zone predominance, and secondly, the presence of pulmonary fibrosis on HRCT, defined as reticular opacities with peripheral and basal predominance, honeycombing, architectural distortion, and/or traction bronchiectasis or bronchiolectasis; focal ground-glass opacities and/or areas of alveolar condensation may be associated but should not be prominent.

The first control group consisted of 50 patients with emphysema. Emphysema phenotype was identified by low attenuation areas of more than 5% in at least one of the six lung fields in HRCT, according to the method of Ito et al [9].

The second control group consisted of 34 patients with IPF. IPF was diagnosed according to the The American Thoracic Society (ATS)/The European Respiratory Society (ERS)/The Japanese Respiratory Society (JRS)/The Latin American Thoracic Association (ALAT) consensus statement [10].

Patients with connective tissue disease, occupational history, environmental exposure, or a history of drugs that resulted in interstitial lung disease were excluded.

All procedures performed in this study involving human participants have been reviewed by the Ethics Committee of Shanghai Sixth People's Hospital and have been performed in accordance with the ethical standards of 1964 Helsinki declaration and its later amendments. An informed consent was obtained from all the participants included in the study.

Identification of polymorphisms in the *MMP-9* gene (NCBI accession number: NG_011468)

Genomic DNA was extracted from whole blood using Blood DNA Midi Kit (Omega, Norcross, GA, USA). The polymorphic region of the *MMP-9* gene was amplified by polymerase chain reaction (PCR) using PCR amplification kit (TaKaRa, Kyoto, Japan) according to the manufacturer's instructions. The primers used were: sense, 5′- GCC TGG CAC ATA GTA GGC CC-3′; antisense, 5′- CTT CCT AGC CAG CCG GCA TC-3′. PCRs were initially denatured at 94°C for 5 minutes and subjected to 35 cycles of amplification in an Applied Biosystems Veriti Thermal Cycler (Applied Biosystems, Foster City, CA, USA) with 20 seconds of denaturing at 94°C, 30 seconds of annealing at 59°C, and 30 seconds of extension at 72°C, followed by a final extension of 72°C for 2 minutes. Amplified DNA was digested with the restriction enzyme SphI (New England BioLabs, Beverly, MA) to detect the allelic variants of *MMP-9* C-1562T. Digested products were electrophoresed on 2% agarose gel and visualized by ultraviolet fluorescence after ethidium bromide staining. The T allele was identified with the 188-bp and 247-bp fragments and the C allele with the undigested product of 435 bp.

Identification of polymorphisms in the *TGF-β1* gene (NCBI accession number: NG_013364)

Genomic DNA was extracted from whole blood. Amplification-refractory mutation system—PCR was used to

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