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ORIGINAL ARTICLE

Association of Pentraxin 3 with Autoimmune Diseases: A Systematic Review and Meta-Analysis

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Background and Aims. Pentraxin 3 (PTX3) plays an important role in the inflammatory processes. Recently it has been reported to be involved in autoimmune diseases. Many studies have investigated the serum/plasma levels of PTX3 in autoimmune diseases, but the results are contradictory or inconclusive among those findings. The purpose of this meta-analysis was to investigate whether serum/plasma levels of PTX3 were associated with autoimmune diseases by comparing the serum/plasma levels of PTX3 in the autoimmune diseases and healthy controls.

Methods. PubMed, ELSEVIER ScienceDirect and Cochrane Library databases (up to December 26, 2015) were used to obtain all relative published literatures. The study quality was assessed by the Newcastle-Ottawa scale. Pooled standard mean difference (SMD) with 95% confidence interval (CI) was calculated by random-effect model analysis.

Results. A total of 20 studies including seven studies of systemic lupus erythematosus (SLE), four studies of ankylosing spondylitis (AS), five studies of rheumatoid arthritis (RA), three studies of systemic sclerosis (SSc) and one study of multiple sclerosis (MS) were finally included in the meta-analysis. The results revealed that the serum/plasma levels of PTX3 in autoimmune diseases were significantly higher than in normal controls (SMD = 0.496 ng/mL, 95% CI = 0.107−0.886, $p < 0.001$; $I^2 = 91.9$, $p < 0.001$). The subgroup analysis showed that the serum/plasma levels of PTX3 in AS and SSc were higher than in healthy controls (pooled SMD = 0.926 ng/mL, 95% CI = 0.174−1.677, $p < 0.001$, $I^2 = 77.0$, $p = 0.013$; pooled SMD = 0.546 ng/mL, 95% CI = 0.136−0.957, $p < 0.001$; $I^2 = 30.9$, $p = 0.299$, respectively).

Conclusions. Serum/plasma levels of PTX3 in autoimmune diseases were higher than in normal controls. © 2016 IMSS. Published by Elsevier Inc.

Key Words: Pentraxin 3, Autoimmune diseases, Inflammation, Fibrosis, Meta-analysis, Serum/plasma levels.

Introduction

Autoimmune diseases are complex chronic inflammatory diseases characterized by immunologic tolerance to self-antigens and immune-mediated tissue destruction. The estimated incidence of autoimmune diseases was 4−5% of the population and females usually demonstrate a higher incidence than males (1). The pathogenesis of autoimmune diseases is not completely understood, but evidence has suggested that genetic and environmental factors may be associated with the pathogenesis of autoimmune diseases (2,3).

Pentraxin 3 (PTX3), also called tumor necrosis factor-stimulated gene 14 (TSG14), is a long pentraxin with 381 amino acids, which belongs to the pentraxin family (4). It shares the C-terminal pentraxin domain with

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short-pentraxins such as C-reactive protein (CRP) and serum amyloid P component (SAP). PTX3 gene is located on human chromosome 3 band q25. The proximal promoter has many transcription factor binding sequences such as nuclear factor-κB (NF-κB), NF-IL-6, AP-1. The NF-κB binding site is essential for PTX3 gene transcriptional activity (5). PTX3 mRNA is strongly induced in response to inflammatory signals mediated by interleukin-1 and tumor necrosis factor-alpha (TNF-α) (6,7). In the inflammatory process, PTX3 is widely produced by many cell types such as macrophages, dendritic cells, fibroblasts, activated endothelial cells, smooth muscle cells (6). IFN-γ and IL-10 exert as regulators of PTX3. IFN-γ inhibits PTX3 production in dendritic cells, monocytes, and macrophages, whereas IL-10 is reported to amplify its LPS-dependent expression (8). Moreover, the production of PTX3 is also regulated by hormones and vitamins such as dexamethasone, prostaglandin E2, 1,25-dihydroxyvitamin D3 (8). However, anti-inflammatory cytokines (IL-4, IL-13) and other cytokines such as IL-6, IL-17, and monocyte chemotactic protein-1 seem not to affect the production of PTX3 (9). As a modulator of inflammatory processes, PTX3 plays an important role in innate immunity, vascular integrity, and fertility as well as inflammation and autoimmunity. In innate immunity, PTX3 plays a special role in the clearance of apoptotic cells and in the regulation of self-antigen presentation as well as influencing cytokine production and innate resistance to selected pathogens (5). In vascular integrity, PTX3 modifies angiogenesis and atherosclerotic lesion development and participates in extracellular matrix formation (10). In addition, PTX3 is also reported to promote fibrocyte differentiation and collagen deposition in murine models of lung fibrosis (11). Recently, numerous studies have focused on the serum levels of PTX3 in autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), ankylosing spondylitis (AS), systemic sclerosis (SSc), and multiple sclerosis (MS) and found that the serum levels of PTX3 were altered in autoimmune diseases (12–28). However, these results are contradictory or inconclusive among those findings.

In this study, a meta-analysis and literature review was performed to comprehensively evaluate the relationship between serum levels of PTX3 and autoimmune diseases and explore possible roles of PTX3 in the physiopathology of autoimmune diseases.

Materials and Methods

Publication Search

A systematic literature search was performed using the PubMed, ELSEVIER ScienceDirect and Cochrane Library databases to locate all relevant publications that documented the association of serum levels of PTX3 in SLE, AS, RA, SSc and MS. Search terms and key words were used as follows: 'Systemic Lupus Erythematosus' or 'SLE' or 'Rheumatoid Arthritis' or 'RA' or 'Ankylosing Spondylitis' or 'AS' or 'Systemic Sclerosis' or 'SSc' or 'Scleroderma' or 'Multiple Sclerosis' or 'MS' combined with 'PTX3' or 'Pentraxin 3'. No language, country, or race restrictions were applied. We recruited data only from the full-published paper and meeting or conference abstracts were excluded.

Inclusion Criteria

Studies meeting the following criteria were considered to be included in this meta-analysis: a) case-control study, clinical cohort or cross-sectional studies design; b) human subjects with SLE or RA or AS or SSc or MS; c) detailed data about plasma/serum level of PTX3 in both patients and healthy controls was accessible. If a study was reported in more than one publication, the latest paper was considered in our meta-analysis.

Exclusion Criteria

Exclusion criteria were as follows: a) conference abstracts, review articles and case reports; b) original papers that did not contain precise plasma/serum levels of PTX3 in patients or controls; c) studies were not performed in humans; d) duplicate reports or data description was ambiguous.

Literature Quality and Data Extraction

A quality score was calculated to assess the methodology quality of all included studies using the Newcastle-Ottawa quality assessment scale (NOS) (29). The NOS scale mainly includes three aspects: participant selection, comparability of subject and ascertainment for the exposure. It consists of eight questions with nine possible points. A higher score represents better quality in methodology. The extracted information for each eligible papers included first author's name, publication year, country of origin, study type, study subjects (sample size, age), source of controls, assay methods of serum PTX3 levels measured, p values of the estimated effects and data of mean PTX3 values (± standard deviation) or median (quartiles). If original important data were unavailable, we contacted the corresponding author by e-mail to obtain further details.

Statistical Analysis

Stata 11.0 software was used for statistical analysis. The effect size of each study was calculated by the standardized mean difference (SMD). SMD and 95% CIs were described by a forest plot. In most studies, the mean and deviation were obtained, but in several studies only the median and quartiles were reported. Therefore, when the original data were median and quartiles, we transformed and calculated the data to gain the appropriate values (30). Cochrane Q test