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Similarity of autoimmune diseases based on the profile of immune complex antigens

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Abstract

Since immune complexes (IC) are a direct product of immune response through the binding between antigen and antibody, the profile of antigen-associated ICs may depend on each autoimmune disease. In this report, we examined the similarity of four neurological autoimmune diseases, Alzheimer's disease and healthy donors, and seven connective tissue diseases based on the profiling of IC-associated antigens which were previously or recently identified by immune complexome analysis of cerebrospinal fluid (CSF) or serum samples. The similarity between each pair of two diseases was assessed by correlation coefficients as distance matrix with the use of detection frequency (i.e., the percentage of patients who were positive for a certain antigen in each disease) of each IC-associated antigen in a certain disease. Among 15 pairs of five diseases and healthy control examined by the analysis of CSF samples, only 1 pair of neuropsychiatric systemic lupus erythematosus and multiple sclerosis corresponds to the higher correlation value ($r=0.73$) than 0.7. On the other hand, among seven connective tissue diseases examined by the analysis of serum samples, 12 of 21 pairs show high correlation value ($r>0.70$). Our finding suggested that the profile of IC-associated antigens identified by immune complexome analysis of CSF samples can be useful for evaluating the similarity of neurological autoimmune diseases; however, not by that of serum samples.

Keywords Autoimmune disease · Immune complexome analysis · Immune complex · Similarity

Introduction

Immune complexes (ICs) are products of reactions that involve non-covalent interactions between foreign antigens or autoantigen and antibody molecules. For a long time, ICs were thought to represent a common pathway for pathogenesis of several diseases (infections, vasculitis and connective tissue autoimmune disorders). Actually, the concentration of circulating ICs (CICs) in sera from patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), or systemic scleroderma (SSc) was significantly higher than those in sera from healthy controls [1]. Many researchers have investigated the mechanisms by which ICs underlie pathogenicity [2–5]. Moreover, ICs may sensitively and faithfully reflect pathophysiological changes that occur at an early stage or during progression of a disease. The profile of antigens-associated ICs may depend on each autoimmune disease; however, profiles on some of diseases may be similar and so, profiling of ICs may be used for evaluating the disease similarity in autoimmune diseases.

In this report, we examined the similarity of neurological autoimmune diseases (neuropsychiatric systemic lupus erythematosus (NPSLE), multiple sclerosis (MS), neuromyelitis optica (NMO), Hashimoto's encephalopathy), neurological non-autoimmune diseases (Alzheimer's disease (ALZ)), and connective tissue diseases (antineutrophil cytoplasmic antibody-associated vasculitis (AAV), Takayasu's arteritis (TA), mixed connective tissue disease (MCTD), dermatomyositis (DM), Sjögren's syndrome (SS), systemic scleroderma (SSc) and systemic lupus erythematosus (SLE)). This examination was based on the profiling of IC-associated antigens which were previously or recently identified by immune complexome analysis, that comprehensively identifies IC-associated antigens [6], of cerebrospinal fluid (CSF) or serum samples and were

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reported in our previous publications [7, 8]. This report focuses on investigating how different profiles of IC-associated antigens are among CNS autoimmune diseases (using CSF) or among connective tissue diseases (using serum) and examining if the different profile of IC-associated antigens is used to distinguish between diseases.

Materials and methods

CSF and serum samples

CSF samples had been collected from each patient; 74 patients with NPSLE ($n=26$; 20–50 years; 26 female), MS ($n=15$; 28–70 years; 10 female), NMO ($n=16$; 29–80 years; 12 female), Hashimoto's encephalopathy ($n=7$; 65–88 years; 5 female), or ALZ ($n=10$; 53–80 years; 7 female) at Nagasaki University Hospital who fulfill their each criteria [7].

Serum samples had been collected from 66 patients; each patient had AAV ($n=7$; 35–86 years; 3 female), TA ($n=7$; 28–63 years; 7 female), MCTD ($n=9$; 43–77 years; 9 female), DM ($n=8$; 30–69 years; 6 female), SS ($n=14$; 35–78 years; 14 female), SSc ($n=7$; 55–78 years; 6 female), or SLE ($n=14$; 16–67 years; 13 female) as diagnosed based on classification criteria [8].

All the samples had been subjected to replicate analyses in accordance with the Helsinki Declaration, with approval from the institutional ethics committees of the Graduate School of Biomedical Sciences (26–8, May 2010), Nagasaki University, and with written informed consent obtained from each patient in our previous studies [7, 8].

Profiling of immune complex-associated antigens

CICs were purified by magnetic beads with immobilized Protein G (PureProteome®, Millipore, Darmstadt, Germany). The tryptic digestion procedure and nano-liquid chromatography–tandem mass spectrometry analysis were performed as previously [6–8].

The similarity between each pair of two diseases (e.g., NPSLE vs MS, AAV vs TA) was assessed by correlation coefficients as distance matrix (Microsoft Excel®) with the use of detection frequency (i.e., the percentage of patients who were positive for a certain antigen in each disease) of each IC-associated antigen in a certain disease. In this study, the pairs with both higher correlation coefficient than 0.7 and lower p value than 0.05 (Student t distribution) were considered to have a significant similarity between the two diseases.

Results

At first, we examined the similarity of NPSLE, MS, NMO, Hashimoto's encephalopathy and ALZ by the analysis of CSF samples from each disease. Of antigens identified, 122 proteins which were identified with two or more samples were enrolled in this examination. The identity of each antigen had been listed in our recent publication [7]. The similarity between two diseases was evaluated with a linear correlation coefficient of detection frequency. Table 1 contains the list of correlation values for all the pairs (15 pairs) of diseases analyzed. It can be seen that only one pair of NPSLE and MS corresponds to the higher correlation value ($r=0.73$) than 0.7. This pair also had a lower p value than 0.05.

Next, based on 185 IC-associated antigens identified by immune complexome analysis of serum samples from seven connective tissue diseases, we examined the similarity of those diseases. As shown in Table 2, 12 of 21 pairs show a high correlation value ($r>0.70$).

Discussion

In clinical, MS, a chronic autoimmune inflammatory disease affecting CNS, is sometimes difficult to be distinguished from NPSLE. An overlap diagnosis often referred to as lupoid sclerosis has been described [9]. They have similar symptoms, such as headache, psychiatric symptom, convulsion, cerebrovascular accident and impaired consciousness. Also, ages of onset are young women and B-cell activity is pivotal in both NPSLE and MS. As a diagnostic sign of MS, but also in some cases of NPSLE, intrathecal immunoglobulin production is present and can be measured as elevated levels of immunoglobulin and/or as oligoclonal immunoglobulin bands in the CSF [10–12]. Based on these findings, our result suggesting the high similarity between NPSLE and MS is thought to be acceptable; profiling of ICs in CSF can be useful for evaluating the similarity of neurological autoimmune diseases. On the other hand, for ICs in serum, the high values ($r>0.70$) obtained in many pairs meant that immune complex-based grouping cannot be used for

Table 1 Fifteen disease–disease coefficients

	NPSLE	NMO	MS	Hashimoto	ALZ
NPSLE	–	–	–	–	–
NMO	0.64	–	–	–	–
MS	0.73	0.60	–	–	–
Hashimoto	0.51	0.64	0.29	–	–
ALZ	0.53	0.59	0.31	0.47	–

Table 2 Twenty-one disease–disease coefficients

	AAV	TA	SSc	MCTD	DM	SLE	SS
AAV	–	–	–	–	–	–	–
TA	0.87	–	–	–	–	–	–
SSc	0.69	0.74	–	–	–	–	–
MCTD	0.82	0.85	0.77	–	–	–	–
DM	0.76	0.71	0.70	0.82	–	–	–
SLE	0.57	0.70	0.60	0.66	0.64	–	–
SS	0.71	0.70	0.69	0.79	0.76	0.8	–

evaluating the similarity between diseases in the analysis of serum. This feature should be because much abundant serum proteins (globulins) mask the difference of minor proteins (antigen proteins). This interference from globulins was supported by the difference of total ion chromatograms between CSF and serum, in which huge peaks derived from globulins are apparent in chromatogram of serum [7].

The profile of IC-associated antigens identified by immune complexome analysis of CSF samples may be used to evaluate disease similarity; however, not by that of serum samples. In diagnosis of autoimmune diseases, some patients are difficult to be categorized into a certain autoimmune disease. Given that the pathogenesis of autoimmune diseases is driven by the presence of autoantigens, profiling of such antigens should be useful to evaluate disease similarity and difference. Furthermore, the autoantigen profiling will be more useful for diagnosis of autoimmune diseases if the profiling includes the information of autoantigen quantities. Our finding indicates that a CSF sample is adequate for the purpose although this study employs the detection frequency of each autoantigen to evaluate disease similarity.

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Author contributions MB and KO analyzed the data and drafted the paper. KI, MT and AK designed and supervised the study.

Compliance with ethical standards

Conflict of interest No potential conflicts of interest were disclosed by all the authors.

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