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Different Coexpressions of Arthritis-Relevant Genes between Different Body Organs and Different Brain Regions in the Normal Mouse Population

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Abstract

Structural changes in different parts of the brain in rheumatoid arthritis (RA) patients have been reported. RA is not regarded as a brain disease. Body organs such as spleen and lung produce RA-relevant genes. We hypothesized that the structural changes in the brain are caused by changes of gene expression in body organs. Changes in different parts of the brain may be affected by altered gene expressions in different body organs. This study explored whether an association between gene expressions of an organ or a body part varies in different brain structures. By examining the association of the 10 most altered genes from a mouse model of spontaneous arthritis in a normal mouse population, we found two groups of gene expression patterns between five brain structures and spleen. The correlation patterns between prefrontal cortex, nucleus accumbens, and spleen were similar, while the associations between the other three parts of the brain and spleen showed a different pattern. Among overall patterns of the associations between body organs and brain structures, spleen and lung had a similar pattern, and patterns for kidney and liver were similar. Analysis of the five additional known arthritis-relevant genes produced similar results. Analysis of 10 nonrelevant-arthritis genes did not result in a strong association of gene expression or clearly segregated patterns. Our data suggest that abnormal gene expressions in different diseased body organs may influence structural changes in different brain parts.

Keywords

Association; Brain structure; Gene expression; Organs

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Introduction

We used a mouse model to explore the possibility of the effect of chronic disease of body organs (e.g., arthritis) on brain structure by examining the association of gene expression between body organs and brain parts. Especially in recent years [1–5], structural changes have been known to exist in different parts of the brain in patients of inflammatory and autoimmune diseases, such as rheumatoid arthritis (RA). The mechanism underlying those changes remains unclear.

It has been reported that prolonged rheumatic diseases cause structural changes of the brain. The changes in different parts of the brain are different [2–5]. In a study investigating brain involvement in RA, Hamed et al. [2] examined markers of brain involvement in 55 females with RA and concluded that the disease process (inflammation and demyelination) was associated with cognitive deficits observed with RA. Wartolowska and colleagues [4] compared imaging data from 31 patients with RA and 25 age- and sex-matched healthy control subjects. The researchers observed an increase in gray matter content in the basal ganglia of RA patients, mainly in the nucleus accumbens and caudate nucleus. In another report, Tzarouchi and colleagues [5] reported that, in comparison with the controls, patients with primary Sjögren syndrome had decreased gray matter volume in the cortex, deep gray matter, and cerebellum. Associated loss of white matter volume was observed in areas corresponding to gray matter atrophy and in the corpus callosum.

The mechanism underlying structural changes in different parts of the brain of RA patients has yet to be understood. Kapadia and Sakic [1] pointed out that structural brain damage induced by chronic autoimmune and/or inflammatory processes is largely the result of the vast complexity of neuroendocrine and immune systems; most of the principal pathogenic circuits are far from being elucidated.

One possibility of different changes in different parts of the brain in RA patients is the result of the changes of gene expression levels of arthritis-relevant genes. If this is true, the changes of gene expression levels caused by arthritis in different parts of the brain should be different. We assumed that such difference is caused by the difference of gene expression in body organs. Thus, the difference in the gene expression in body organs is caused by RA. We hypothesized that the expressions of disease-relevant genes between different parts of the brain and body organs are differently associated in the absence of disease; therefore, when chronic diseases or illness of body organs occurred in those body organs, the disease-relevant genes caused damage to different brain parts differently. To test our hypothesis, multiple sets of gene expression data from a large number of individuals in the same population were needed. The multiple data sets needed to include the gene expression profiles from different brain parts, as well as from different body organs. Such human data sets currently are not available. They are also rare in animal models. We took advantage of GeneNetwork (<http://www.genenetwork.org/webqtl/main.py>) and analyzed the expressing association of 20 genes between five parts of the brain and body organs (spleen and other organs) in a population of recombinant inbred (RI) mouse strains derived by crossing C57BL/6J (B6) and DBA/2J (D2) [6].

Results

Correlation between expression of upregulated and downregulated genes in arthritis and genes between different parts of brain and different body organs

The expressions of five upregulated and five downregulated genes in spleen and other body organs were highly correlated to the expression in five parts of brain (Supplementary Table S1). However, the total association values of 10 genes between organs and five parts of the brains were different (Figure 1). The association values of spleen to brain parts and lung to brain parts were similar, with positive values of $Tr = 6.4648$ and $Tr = 5.1353$, respectively. The Tr values of kidney and brain parts and liver and brain parts, however, were different. The Tr value of kidney and brain parts was -6.7904 , while the Tr value of liver and brain parts was 0.9992 .

A close examination of the correlation patterns of gene expression levels between spleen and brain parts suggested that the correlation patterns of 10 genes between spleen and five parts of the brain had two kinds of patterns (Figure 2). The correlations between spleen and three brain parts (cerebellum, striatum, and hippocampus) had almost the same pattern (Figure 2A), while the pattern of prefrontal cortex and nucleus accumbens were very similar (Figure 2B).

The overall association of three other body organs with brain parts showed different similarities compared to that of spleen (Figure 3). In spleen, the correlation of seven genes (Adipoq, Dcn, Ednrb, Ccr2, Usp12, Adamdec1, and Camk2b) between spleen and five parts of the brain was similar (Figure 3A); the correlation patterns of Car3, Skap1, and Slc4a1 between spleen and prefrontal cortex and nucleus accumbens were similar (Figure 3A). By comparing their correlations with brain parts, the patterns between spleen and lung were quite similar (Figure 3A and 3B), while the patterns of kidney and liver showed differences to that of spleen (Figure 3C and 3D).

Correlation between expression of arthritis-relevant genes in different parts of brain

We next compared the association of gene expression of five known arthritis-relevant genes in organs to brain parts. The overall association Tr values of spleen and lung to brain parts were negative, while the values of kidney and liver were positive (Figure 4). Most individual r values of every gene between spleen and brain parts were negative (Figure 5A). Among five genes, association of expression of CD4 between spleen and five parts of the brain showed different patterns. While the association between three parts (prefrontal cortex, nucleus accumbens, and striatum) and spleen was highly positive, the association between hippocampus and spleen was highly negative. There was no association between cerebellum and spleen for the expression of CD4. While most individual r values of lung were similar to that of spleen (Figure 5B), the association of expression of CD5 appeared to be different. Most of the r values of kidney and liver, however, were positive (Figure 5C and 5D), while CD4 expression was similar to that of spleen.

The data from up- and downregulated genes of an arthritis mouse model suggested that the associations of expression of arthritis-relevant genes between arthritis-relevant organs, such

as spleen and lung, were closer than were associations of organs that were not arthritis relevant.

Correlation between expression of genes known to be unconnected to arthritis and genes in different parts of brain

The expression of those 10 nonarthritis-relevant genes in spleen showed a much weaker correlation to the expression of five parts of the brain (Figure 6) in comparison to that of arthritis-relevant genes mentioned in above. The range of r values was from -0.2174 to 0.9845 , while most r values fell between -0.2 and 0.5 (Figure 6). Furthermore, the correlations between expression levels of the 10 nonarthritis-related genes between spleen and five parts of the brain did not have clearly segregated patterns.

Discussion

Our analysis showed that expression levels of arthritis-relevant genes in body organs were differently correlated to different parts of brain. In particular, the arthritis-relevant genes were highly correlated with disease-affected body organs (e.g., spleen and lung) and different brain structures (e.g., prefrontal cortex and nucleus accumbens) with unique patterns [1]. Thus, our data suggest that prolonged abnormal expressions of certain genes in the spleen and lung affect structural changes in certain brain parts by affecting the gene expression of those parts of the brain. Our data are the first step towards understanding the molecular mechanism of structural changes of RA patient brains.

Our data also show that expression levels of arthritis-relevant genes in the same organ correlated differently to the expression levels in different parts of the brain. The data agree with the findings in humans that changes in different brain structures in patients of arthritis are different [2–5]. They further suggest that the disease in one body organ affects differently different parts of the brain. These initial, but very important, data need to be confirmed by further studies using animal models or investigations in other chronic diseases.

Our analysis of the nonarthritis genes indicated that the correlations between those genes and genes in brain parts are not significantly correlated, and there is no distinguishable pattern among different parts of the brain. Thus, non-RA-relevant genes will not differentially affect structural changes in brain parts. Altogether, our data suggest that the morphologic changes in different parts of the brain in RA patients may be caused by the interaction between arthritis-relevant genes in spleen or lung and in brain. The difference in gene expression associations may lead to differences in structural changes in different parts of brain. The classic paradigm [7–9] has let us study different parts of the brain for their controlling mechanisms of activity of body parts or organs (e.g., cerebellum controlling movement). Our study is the converse of this paradigm. Our data suggest that activities of disease status of an organ or a body part can affect brain structure.

Ideally, gene expression levels from tissues directly affected by disease (e.g., synovial tissue) should be used for such analysis. However, gene expression data from different parts of the brain and different body organs from the same relatively large population are currently not available. We selected arthritis-relevant genes based on our data from previous

experiments and experience. We first selected five of the most upregulated genes and five of the most downregulated genes in a mouse model of spontaneous arthritis from our previous data [10] in which we produced whole-genome gene expression profiles of a mouse model of spontaneous arthritis. We then selected five genes known to be arthritis relevant based on publications from PubMed. We realize that those genes may not represent all the arthritis-relevant genes. A study with a much more complete gene list may be necessary to obtain a definitive result of organ and brain relationships in RA patients. The selection of 10 nonarthritis-relevant genes is based on only the literature. Thus, the selection criterion was that those genes had not been reported to have function related to arthritis. However, some, or any, of them may be found to be arthritis-relevant genes in the future.

It is known that immune genes interact with neurological genes. However, knowledge of such a connection is not clear. Our study sought to bridge the gap between the expression of disease genes and genes in particular parts of the brain. Accordingly, we speculated that abnormal expression of genes of major chronic diseases can be connected to different parts of brain; therefore, the effect of major chronic diseases on body organs can be mapped to different parts of brain. However, our study is only the first step in this fundamental issue. Further testing of our hypothesis will increase our understanding of the molecular basis for the connection between brain and diseases.

Materials and Methods

Arthritis-relevant and -nonrelevant genes

We first selected genes for comparison from our previous study [10] in which we analyzed the expression patterns of arthritis in 38 individuals in a mouse F2 population and compared the expression levels of key candidate genes to the parental strains. We first selected the five most downregulated genes in spontaneous arthritis (Table 1): adiponectin (Adipoq), carbonic anhydrase 3 (Car3), decorin (Dcn), endothelin receptor type B (Ednrb), and src family-associated phosphoprotein 1 (Skap1). We then selected five of the most upregulated genes in spontaneous arthritis in mice (Table 1): chemokine (C-C motif) receptor 2 (Ccr2), ubiquitin-specific protease 12 (Usp12), ADAM-like decysin 1 (Adamdec1), solute carrier family 4 (anion exchanger) member 1 (Slc4a1), and calcium/calmodulin-dependent protein kinase II beta (Camk2b).

We next selected five known arthritis-relevant genes to analyze their association between body organs and brain structures (Table 1): Fc receptor, IgG, high affinity I (Fcgr1); histocompatibility 2, class II antigen A, alpha (H2-Aa); CD4 antigen (Cd4); Tnf receptor-associated factor 1 (Traf1); and interleukin 17A (Il17a). The relevance of those genes to arthritis has been reported in multiple publications.

We finally included 10 nonarthritis-related genes for analysis (Table 1): carbonic anhydrase 3 (Car8); intracellular chloride channel 6 (Clc6); potassium channel, inwardly rectifying, subfamily j, member 1 (Kcnj1); myogenic factor 6 (Myf6); Sh3 and multiple ankyrin repeat domains 3 (Shank3); bone morphogenetic protein 1 (Bmp1); chloride intracellular channel 6 (Clc6); potassium inwardly-rectifying channel, subfamily J, member 1 (Kcnj1); activating transcription factor 2 (Atf2); and glutathione S-transferase, mu 3 (Gstm3). The definition of

nonarthritis-relevant was determined by no direct function in arthritis of those genes in the PubMed database searched on April 20, 2012, and using the name of each gene and key word “arthritis”.

Gene expression data from GeneNetwork database

Gene expression profiles were obtained from GeneNetwork (<http://www.genenetwork.org/webqtl/main.py>). We used the gene expression profiles generated by Affymetrix chip M430.v2 (www.affymetrix.com) of various tissues. RNAs for the gene expression profiling were from recombinant inbred (RI) strains derived by crossing C57BL/6J (B6) and DBA/2J (D2) and inbreeding progeny for 20 or more generations [3]. The microarray data in the GeneNetwork database were generated by a large number of investigators over several years (details for each set of data can be found at <http://www.genenetwork.org/webqtl/main.py>). Based on the availability of data from the same platform and relevance to this study, we compared expression profiles of some genes from B6 × D2 RI strains in the following tissues: spleen, lung, kidney, liver, striatum, prefrontal cortex, nucleus accumbens, hippocampus, and cerebellum.

Spleen data set

Spleen mRNA expression levels were measured in 77 individual BXD RI mice from 24 different strains. Spleens of female BXD mice were harvested between 8 and 12 weeks of age and were used for microarray analysis using Affymetrix GeneChip Mouse Genome 430 2.0 Array (see detailed information at http://www.genenetwork.org/dbdoc/IoP_SPL_RMA_0509.html).

Lung data set—Lung expression data set included 47 BXD strains. Total RNA was extracted from the lungs by using RNA STAT-60 (Tel-Test, Inc.). RNA from two to five animals per strain were pooled and used for gene expression analysis. Animals used in this study were between 49 and 93 days of age. All inbred strains were profiled for both sexes; for a given BXD strain, either males or females were used (detailed information in [11]).

Kidney data set—The July 2006 Kidney QTL Consortium data set provided mRNA expression in the adult kidney of 54 BXD RI strains. This particular data set was processed using the position-dependent nearest neighbor model (PDNN) protocol (detailed information can be found at http://www.genenetwork.org/dbdoc/MA_M2_0806_P.html).

Liver data set—Male mice in BXD strains for this study were from The Jackson Laboratory. Mice were between 6 and 10 weeks of age; to ensure adequate acclimatization to a common environment, the mice were maintained until 16 weeks of age (see [12] for complete information).

Striatum data set—This April 2005 data (developed by Dr. Rosen at Beth Israel Deaconess Medical Center (BIDMC) at Harvard University) freeze provided estimates of mRNA expression in the striatum (caudate nucleus of the forebrain) of 31 lines of mice including C57BL/6J, DBA/2J, and 29 BXD RI strains. Animals were obtained from The Jackson Laboratory and housed for several weeks at BIDMC until they reached ~2 months

of age (detailed information can be found at http://www.genenetwork.org/dbdoc/SA_M2_0405_PC.html).

Prefrontal cortex data set—This BXD data set provided estimates of mRNA expression in the prefrontal cortex following ethanol treatment across 27 BXD recombinant inbred strains and their B6 and D2 progenitor strains (detailed information can be found at http://www.genenetwork.org/webqtl/main.py?FormID=sharinginfo&GN_Accession Id=136).

Nucleus accumbens data set—The data set was from female mice at 2 months of age. No detailed information is provided at GeneNetwork.

Hippocampus data set—The Hippocampus Consortium data set provided estimates of mRNA expression in the adult hippocampus 67 BXD RI strains. A pool of dissected tissues, typically from six hippocampi and three naive adults of the same strain, sex, and age, was collected in one session and used to generate cRNA samples (detailed information can be found at http://www.genenetwork.org/webqtl/main.py?FormID=sharinginfo&GN_Accession Id=112).

Cerebellum data set—This May 2005 data freeze provided estimates of mRNA expression in adult cerebellum of 28 BXD RI strains (detailed information can be found at http://www.genenetwork.org/dbdoc/GCB_M2_0505_M.html).

Association analysis using correlation r value

We analyzed the correlations between the expression levels of each gene in body organs and in brain tissues in the BXD population, which lacked disease. For the expression level of each gene, we collected data of every probe of every gene. Because the gene expression profiles were generated by the same microarray platform, Affymetrix, the expected number of probes for each gene in different tissues was the same. The correlation between the expressions of a gene in two tissues, such as spleen and nucleus accumbens, was determined by the r value, with 1 as the maximum positive value and -1 as the maximum negative correlation. The total association of genes between two tissues was defined as the average of values of R (Tr).

$$Tr = \Sigma(r_1 \dots r_n) \quad (\text{Formula 1})$$

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviation list

RA	rheumatoid arthritis
D2	DBA/2J
B6	C57BL/6J
RI	recombinant inbred
Adipoq	adiponectin
Car3	carbonic anhydrase 3
Dcn	decorin
Ednrb	endothelin receptor type B
Skap1	src family-associated phosphoprotein 1

Ccr2	chemokine (C-C motif) receptor 2
Usp12	ubiquitin-specific protease 12
Adamdec1	ADAM-like decysin 1
Slc4a1	solute carrier family 4 (anion exchanger) member 1
Camk2b	calcium/calmodulin-dependent protein kinase II beta
Fcgr1	Fc receptor, IgG, high affinity I
H2-Aa	histocompatibility 2, class II antigen A, alpha
Cd4	CD4 antigen
Traf1	Tnf receptor-associated factor 1
Il17a	interleukin 17A
Car8	carbonic anhydrase 3
Clic6	intracellular chloride channel 6
Kcnj1	potassium channel, inwardly rectifying, subfamily j, member 1
Myf6	myogenic factor 6
Shank3	Sh3 and multiple ankyrin repeat domains 3
Bmp1	bone morphogenetic protein 1
Clic6	chloride intracellular channel 6
Kcnj1	potassium inwardly-rectifying channel, subfamily J, member 1
Atf2	activating transcription factor 2
Gstm3	glutathione S-transferase, mu 3

Highlights for reviewers

- Examined expression of 10 genes from a mouse model of arthritis in a normal mouse population.
- We found two groups in gene expression patterns between five brain structures and spleen
- Analysis of the five additional known arthritis-relevant genes produces similar results.
- Analysis of 10 nonrelevant arthritis genes did not obtain clearly segregated patterns.

Figure 1.

Tr values of expression of 10 genes between four body organs and brain parts. The Tr values are calculated according to formula 1, in text of materials and methods. The association between spleen and lung to brain tissues is similar. The Y bar indicates the Tr values between body tissues and brain parts.

Figure 2.

Different patterns of correlations of gene expression between spleen and brain structure. Y bar is the Tr values. Figure 2A. The patterns between spleen and three brain structures (cerebellum, striatum, and hippocampus) are the same. Figure 2B. The patterns between spleen and two brain structures (prefrontal cortex and nucleus accumbens) are similar.

Figure 3.

Patterns of r values of overall gene expression between body organs and brain structures. Y bar is the r values of expression of each gene. Figure 3A. Overall correlations between spleen and five brain structures. Figure 3B. Overall correlations between lung and five brain structures. Figure 3C. Overall correlations between kidney and five brain structures. Figure 3D. Overall correlations between liver and five brain structures.

Figure 4.

Overall association of gene expression between four body organs with five brain structure of five known arthritis-relevant genes. Y bar indicates the Tr values between each body organ and brain structures. The overall associations of spleen and lung to the five brain structures are similar, while the overall associations of kidney and liver are similar.

Figure 5.

Patterns of association of gene expression between body organs and brain structures. Y bar indicates the r values of gene expression between the body organ and the brain structures. Figure 5A. Correlation of gene expression between spleen and five brain structures. Figure 5B. Correlation of gene expression between lung and five brain structures. Figure 5C. Correlation of gene expression between kidney and five brain structures. Figure 5D. Correlation of gene expression between liver and five brain structures.

Figure 6.

The patterns of correlations of expression levels of 10 nonarthritis-relevant genes between spleen and five parts of brain. Y bar indicates the r values between spleen and brain parts.

Table 1

Number of probes in microarray analysis in each gene in each tissue

Lung	Cerebellum	Rosen Striatum	Hippocampus Consortium	Nucleus Accumbens	Prefrontal Cortex	kidney	Spleen	liver
Adipoq	2	2	2	2	2	2	2	1
Den	2	2	2	2	2	2	2	1
Ednrb	4	4	4	4	4	4	4	2
Ca3	4	4	4	4	4	4	4	2
Scap1	2	2	2	2	2	2	2	0
Cer2	5	5	5	5	5	5	5	3
Usp12	3	3	3	3	3	3	3	3
Adamdec1	1	1	1	1	1	1	1	1
Slc4a1	3	3	3	3	3	3	3	3
Camk2b	2	2	2	2	2	2	2	2
Fcgr1	2	2	2	2	2	2	2	1
H2-Aa	4	4	4	4	4	4	4	2
Cd4	2	2	2	2	2	2	2	2
Traf1	2	2	2	2	2	2	2	1
Il17a	2	2	2	2	2	2	2	2
Bmp1	4	4	4	4	4	4	4	3
Clec6	2	2	2	2	2	2	2	0
Kenj1	2	2	2	2	2	2	2	2
Atf2	6	6	6	6	6	6	6	4
Gstm3	3	3	3	3	3	3	3	3