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Short Communication

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 the 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.

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1. 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 (Hamed et al., 2012; Kapadia and Sakic, 2011; Kim et al., 2011; Tzarouchi et al., 2011; Wartolowska et al., 2012), 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 (Hamed et al., 2012; Kim et al., 2011; Tzarouchi et al., 2011; Wartolowska et al., 2012). In a study investigating brain involvement in RA, Hamed et al. (2012) 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 et al. (2012) 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 et al. (2011) 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

Abbreviations: 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.

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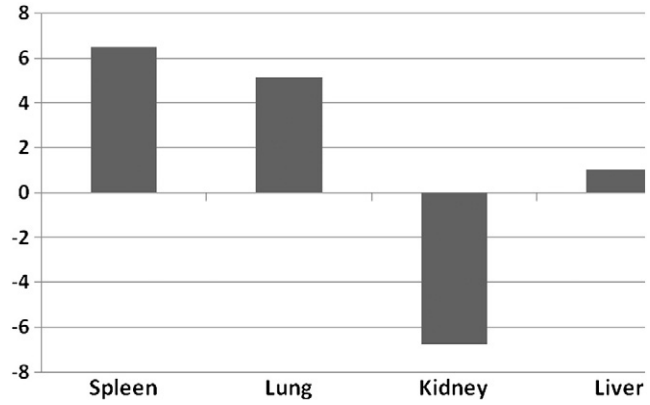

Fig. 1. Tr values of expression of 10 genes between four body organs and brain parts. The Tr values are calculated according to formula 1, in text of materials and methods. The association between spleen and lung to brain tissues is similar. The Y bar indicates the Tr values between body tissues and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

(2011) 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) (Philip et al., 2010).

2. Results

2.1. 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

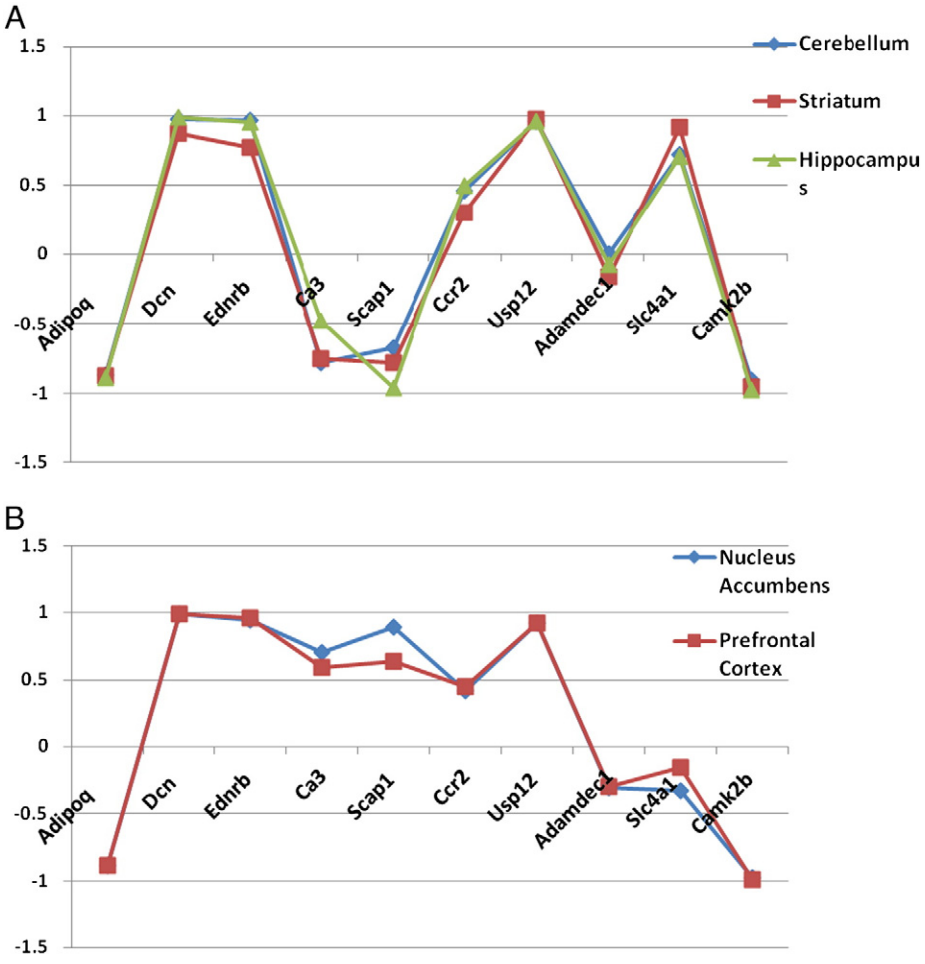

Fig. 2. Different patterns of correlations of gene expression between spleen and brain structure. Y bar is the Tr values. Fig. 2A. The patterns between spleen and three brain structures (cerebellum, striatum, and hippocampus) are the same. Fig. 2B. The patterns between spleen and two brain structures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