Schizophrenia is a TH2 dominant autoimmune disease possibly against acetylcholine receptors of CNS

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Abstract

Schizophrenia is a very common psychiatric disorder. However, its etiology and pathogenesis is still unknown. Current theory saying that neurotransmitter imbalance such as serotonin or dopamine only provides limited effectiveness in schizophrenia treatment by drugs changing serotonin and dopamine concentration. Despite of such treatment, majority of schizophrenia patients still have very poor prognosis. Thus, the neurotransmitter imbalance theory is not correct. Here, I propose that schizophrenia is actually a TH2 dominant autoimmune disorder. The candidate of autoantigen could be acetylcholine receptors of CNS. My theory can explain the positive as well as negative symptoms of schizophrenia. By microarray analysis of PBMCS, one-tenth of the total 519 significantly expressed genes are immune-related genes. Among them, TH2 related genes are significantly up-regulated including IL-4, histidine decarboxylase, aldehyde dehydrogenase, CCR9, IgE Fc receptor, GATA2, serotonin receptor, phospholipase A2, and prostaglandin D2 synthase. Besides, TH1 and TH17 related genes are down-regulated including CXCL5, cathepsin C, and neutrophil related S100 binding proteins. The new theory sheds a light to better control this detrimental illness. Anti-inflammatory agents could be used to manage schizophrenia in the near future.

Introduction

Schizophrenia is the most detrimental psychiatric disease. Its incidence and prevalence are higher in developed countries. Although this illness has a very high impact on global health, its etiology or pathogenesis is still not known. Currently, the most popular theory for schizophrenia etiology is neurotransmitter imbalance theory. The theory says that the imbalance of brain neurotransmitters such as dopamine and serotonin cause the symptoms and signs of schizophrenia. According to this theory, many drugs developed to modify CNS neurotransmitter concentrations to try to control schizophrenia. Even the symptoms of hallucination and delusion are improved a little bit by these agents, the long term prognosis of schizophrenia is still very poor. Thus, the neurotransmitter imbalance theory may not correct. If we don't know the real etiology or pathophysiology of this disease, we cannot use the correct management strategy to control schizophrenia. Here, I use microarray analysis and literature reviews to demonstrate that schizophrenia is actually a TH2 dominant autoimmune disease. Acetylcholine receptor of CNS should be the most likely candidate for the autoantigen.

Material and Methods

Blood samples

Second hand data analysis was performed by using the GEO sample set. In the San Diego sample set, participants were recruited from University of California, San Diego (UCSD) Psychopharmacology Research Initiatives Center for Excellence (PRICE). Inclusion criteria are: 1. Age between 18 and 55 years-old 2.at least eighth-grade education 3. English is their first language 4. No mental retardation. Exclusion criteria are: 1. Substance abuse or dependence 2. Neurological problems such as stroke or meningitis 3. Systemic medical illness such as heart disease or diabetes 4. History of head injury with documented loss of consciousness lasting longer than 10 minutes 5. Pregnancy 6. Physical disabilities.

Whole blood samples (10ml) were collected in the morning after subjects fasted overnight with EDTA-coated collection tubes. Then, peripheral blood mononuclear cells (PBMC) were acquired from LeukoLOCK filter. Eluted mRNA samples from PBMCs were then stored at -20^{o}C until transferred to the GeneChip Microarray Core (San Diego, CA) for microarray hybridization. Final, thirteen schizophrenia samples were hybridized to GeneChip Human Exon 1.0 ST Arrays (Affymetrix, Inc., Santa Clara,

CA).

Microarray analysis

The above microarray hybridization raw data (CEL files) have been uploaded onto GEO (GSE12288). I download these data set and redo the microarray expression significance analysis by using Genespring software. Unpaired student T-test with unequal variance and non-adjusted false discovery rate were used to analyze the data set in Schizophrenic patients' blood samples compared to those of healthy control.

Q-PT-PCR verification

Professor Ian P. Everall et al. did quantitative reverse-transcriptase polymerase chain reaction (QRTPCR) verification for the exon array of the San Diego sample set. Aliquots of each mRNA sample were reverse transcribed to single stranded cDNA using SuperScript III First Strand cDNA Synthesis Kit (Invitrogen Corporation, Carlsbad, CA). Then, 50 ng of cDNA was used as the template in 20ul TaqMan reactions using ABI universal Master Mix primers and probes designed by Applied Biosystems (Foster City, CA). Gene specific standard curves for ARF1 (Assay ID Hs00796826_s1), BAT1 (Assay ID Hs00366447_m1), and GDI2 (Assay ID Hs00357525_m1) were generated. The QRTPCR results of the selected three genes confirmed the microarray analysis of this experiment. Thus, the microarray procedure is validated.

Results

Global gene expression pattern in schizophrenia blood samples

By Genespring analysis, we found 519 significant gene change (both up-regulation and down-regulation). Among the 519 genelist, 50 genes are immune-related. It suggests that host immune response plays an important role in the etiology or pathophysiology of schizophrenia. Thus, about one-tenth of all the significantly expressed genes are immune-related. Immune response plays an important role in schizophrenia.

Special expressed genes in schizophrenia compared to previous association studies

I compare the genelist from the microarray analysis result to previous association

studies. I find out that several schizophrenia-related genes are expressed in this genelist. These genes include serotonin receptor and TCF4. Thus, my analysis is consistent with previous association studies. (Table 1)

Immune-related gene up-regulation in leukocytes of schizophrenia patients

Among the 519 up-regulated or down-regulated genes in peripheral blood of schizophrenic patients, about one-tenth genes are immune-related. This means that host immune response are activated during the happening of schizophrenia. Thus, host immunological pathway is highly associated with the attack of schizophrenia. This result supports that schizophrenia is actually an autoimmune disorder. (Table 2)

Th2 immunological pathway up-regulation in peripheral blood of schizophrenia patients

According to my microarray analysis, many TH2 immune response related genes are up-regulated in schizophrenia. Among this dataset, the key TH2 driven cytokine IL-4 is significantly up-regulated during the attack of schizophrenia. Thus, we can infer that TH2 autoimmunity is activated in schizophrenia. Besides, histidine decaboxylase, the key enzyme for production of histamine, is highly up-regulated in peripheral blood of schizophrenia. Histamine is a key mediator of TH2 immunological pathway. With the up-regulation of IL-4 and histamine, TH2 dominant immune response should happen in schizophrenic patients. (Table3) Besides, many TH2 related genes are up-regulated in schizophrenic patients including carboxypeptidase A3, CXCL5, S100 binding protein A12, CCR9, IgE Fc receptor, reticulocalbin 3, GATA2, integrin alpha 1, interleukin 4, secretary leukocyte peptidase inhibitor, phospholipase A2, cathepsin C, glutathione peroxidase 1, retinol binding protein 2, and prostaglandin D2 synthase.

Discussion

Schizophrenia is very common and detrimental psychiatric disorder. Despite of its importance, the etiology and pathophysiology of schizophrenia is not clearly known. Currently, the most accepted theory for schizophrenia pathogenesis is neurotransmitter imbalance theory. In this theory, imbalance of dopamine, serotonin, and glutamate can account for the happening of schizophrenia. Thus, current medications for schizophrenic patients are drugs to modify the brain concentration

of these neurotransmitters. Despite of this kind of treatment, the prognosis of schizophrenia is still very poor. Majority of schizophrenic patients are severely disabled in their lifetime. Many of them commit suicide because they cannot tolerate the disease progression. The ineffectiveness of neurotransmitter modification suggests that neurotransmitter imbalance is not the actual cause of schizophrenia.

Among these neurotransmitters, dopamine hypothesis is most widely accepted. Several researchers suggested that dopamine system in the mesolimbic pathway may contribute the positive symptoms of schizophrenia such as delusion or hallucination. The excessive dopamine in brain causes the attack of schizophrenia. Certain studies found out that amphetamine and cocaine, two illegal drugs which can lead to schizophrenia symptoms, can increase the brain concentration of dopamine.(Ito 2004; Fox, Esbenshade et al. 2005) Thus, it is the reason of amphetamine psychosis and cocaine psychosis. However, these are several defects of the dopamine hypothesis. Dopamine is a neurotransmitter which is related to motivation. The excessive dopamine may explain the positive symptoms such as hallucination and delusion. Actually, the excessiveness of dopamine in brain usually causes euphoria, alertness, and over-confidence; these symptoms are more reminiscent of mania than schizophrenia. However, the more detrimental negative symptoms such as avolition (lack of motivation) cannot be explained by the excessive dopamine hypothesis. Actually, it is the opposite. PET scan was used to study the brain functional dopamine receptors.(Seok Jeong, Kwon et al. 2005) When schizophrenia patients have 90% block of dopamine D2 receptors by certain antipsychotic agents, these is little reduction of the psychoses behavior. Furthermore, although dopamine inhibiting medications modify dopamine levels within minutes, the positive symptoms of schizophrenia only subside at least several days or even weeks. In addition, the main target of new generation of antipsychotic agents such as clozapine and quetiapine is not dopamine receptors. They bind and unbind dopamine receptors rapidly in brain. Besides, other psychosis inducing agents such as phencyclidine and ketamine don’t have any effect on the brain concentration of dopamine.(Wang, McInnis et al. 2001) Besides the functional anomalies in schizophrenia, there are also anatomical anomalies in schizophrenia such as ventricle enlargement and brain atrophy.(Roberts 1991) Dopamine imbalance cannot explain the pathopsysiology of schizophrenia. However, it is worth noting that dopamine can be secreted by immune cells such as T lymphocytes. Dopamine is a strong immune-mediator suppressing prolactin. Prolactin is usually secreted in late pregnancy to activate Treg cells via STAT5 to suppress maternal immunity.(Gaufo and Diamond 1996; Cosentino, Fietta et al. 2007) Thus, dopamine can suppress the function of regulatory T cells to enhance

lymphocyte immunity. This also links the dopamine's work and autoimmunity in schizophrenia.

Serotonin excessiveness is more likely to be related to the positive symptoms of schizophrenia. LSD, an illegal drug which can modulate brain serotonin concentration, can induce visual or auditory hallucination.(Rivero, Sanjuan et al. 2010) In addition, many new generation antipsychotic agents are serotonin modifiers. It is possible that the hallucination induced by serotonin induce the subsequent delusion in schizophrenia. However, the excessive serotonin still cannot explain the negative symptoms of schizophrenia such as blunt emotion and avolition. It cannot explain the anatomical anomalies such as brain atrophy and ventricle enlargement in schizophrenic patients, either.(Seok Jeong, Kwon et al. 2005) Neurotransmitter imbalance may only explain the functional anomalies but not the anatomical anomalies in schizophrenic patients. Many new generation anti-psychotic agents are 5HT1A antagonists. That suggest that serotonin plays an important role in positive symptoms of schizophrenia such as hallucination and delusion.

Many risk factors have been linked to the incidence of schizophrenia such as genetic inheritance, infection, environmental factors such as drug usage. If we want to link all the risk factors for schizophrenia, autoimmunity is the most likely etiology of schizophrenia. If schizophrenia is a TH2 dominant autoimmune disorder, it can explain many phenomenon seen in schizophrenic patients. The incidence of schizophrenia is higher in the developed countries and urban area. Current theory thinks the stress in industrial nations may aggravate schizophrenia. However, it could be actually the environmental plasticizer concentration is higher in these developed nations. These plasticizers such as DEHP are strong TH2 driving agents. Thus, TH2 related allergic and autoimmune diseases are rising in industrial nations. Many association studies show that acetylcholine receptors such as nicotinic receptors or muscarinic receptors are related to the schizophrenia.(Freedman, Leonard et al. 2001) Actually, these acetylcholine receptors in brain neurons can be the autoantigens for this TH2 autoimmune disease.(Henneberg, Horter et al. 1994; Yang, Chengappa et al. 1994) Thus, these TH2 autoimmune cells can attack CNS neurons by recognizing these cortical acetylcholine receptors. Finally, brain atrophy and ventricle enlargement happen after immune destruction. Only autoimmune mechanism can explain the negative symptoms of schizophrenia. Alpha 7 CNS nicotinic acetylcholine receptor is a widely accepted gene linking to schizophrenia. In postmortem studies, the acetylcholine receptor numbers are severely decreased in schizophrenia patients.(Gault, Hopkins et al. 2003) Autoantibody for alpha 7 CNS nicotinic

acetylcholine receptor is also found in schizophrenia patients.(Chandley, Miller et al. 2009) Tobacco usage is highly associated with the schizophrenia.(Dalack, Healy et al. 1998) It is likely the nicotinic acetylcholine receptors are targeted and damaged by TH2 autoimmune cells. Thus, schizophrenic patients need to smoke to stimulate their nicotinic receptors to maintain brain function. It is worth noting that HSV and CMV antibodies are often found in serum of schizophrenia patients.(Albrecht, Torrey et al. 1980; Yolken and Torrey 1995) Thus, molecular mimicry between viral antigen and brain antigen may play an important role in the pathogenesis of schizophrenia. In a JCI paper, there is cross reactivity between acetylcholine receptor and HSV viral antigen.(Schwimmbeck, Dyrberg et al. 1989) HSV usually causes latency infection of neurons. In addition, HSV encephalitis usually causes symptoms such as hallucination and behavior change. Thus, HSV or CMV could be important causing factor of schizophrenia. Possible dietary antigen is also investigated in schizophrenia patients.(Severance, Lin et al. 2011) An animal model of schizophrenia is DISC1 genetic modified mice.(Hikida, Jaaro-Peled et al. 2007; Mathew, Law et al. 2007) DISC1 and neuregulin 1 are both related to nicotinic acetylcholine receptor. This also matches my hypothesis.

Serotonin is a key mediator in TH2 immunological pathway. The function of serotonin in TH2 immune response is to induce diarrhea in GI tract and to induce bronchospasm to expel the intestinal or bronchopulmonary parasites. Serotonin can also activate T lymphocytes.(Leon-Ponte, Ahern et al. 2007) However, serotonin is also a neurotransmitter. When the TH2 autoimmune cells reach the CNS, they can release a lot of serotonin to brain cortex to cause hallucination and subsequent delusion.(Rivero, Sanjuan et al. 2010) Basophils, mast cells, and TH2 CD4 T cells can also release serotonin.(Abramovitz, Altboum et al. 1991) Thus, this TH2 autoimmunity hypothesis can also satisfactorily explain the positive symptoms of schizophrenia.

Many schizophrenia patients have the sensation of pseudoparasites (delusional parasitosis). They think they have parasite moving in their body such as under the skin. If schizophrenia is a TH2 dominant autoimmune disorder, it can explain this common phenomenon in schizophrenia. TH2 immunological pathway is the host immunity against helminthes parasites. In TH2 immune response, histamine is released by mast cells or basophils to cause the itchiness sensation. Thus, schizophrenic patients will think they are infected by parasites. This kind of “delusion” suggests that schizophrenia is a TH2 autoimmunity.

Another common symptom in schizophrenia is that patients always feel thirsty and drink a lot of water. This can be explained by histamine. In CNS, histaminergic neurons secreting histamine control the desire of thirst.(Ito 2004) Thus, if there are too many histamines in brain, patients will feel extremely thirsty. Histamine is a key effector molecule in TH2 immunity. This phenomenon also suggests that schizophrenia is a TH2 dominant autoimmune illness.

First, schizophrenia patients need to have specific type of HLA to recognize a brain autoantigen such as alpha 7 nicotinic receptor. In addition, accessory molecules play the function like toll-like receptor should be present to trigger TH2 immunological pathway. CNS histaminergic neurons secreting histamine play the key role here. Many schizophrenia inducing agents such as PCP, amphetamine, or cocaine can induce the release of histamine in CNS.(Prell, Green et al. 1995) Then, histamine can favor this autoimmune to the TH2 immunological pathway. Antihistamine treatment of schizophrenia has been studied and it is functional.(Stevens 1962; Fox, Esbenshade et al. 2005) Histamine receptor allele polymorphism is also related to schizophrenia.(Orange, Heath et al. 1996) As long as the presence of the autoantigen and accessory molecule, the TH2 autoimmunity will persist. Serotonin released from TH2 CD4 T cells, basophils, and mast cells causes hallucination and subsequent delusion. Finally, these TH2 autoantibodies and autoimmune T cells can destroy CNS neurons to cause brain atrophy with ventricle enlargement. Due to the CNS neuron death, the negative symptoms such as avolition, poverty of thought, social withdraw, and speech/behavior disorganization will appear in schizophrenic patients. This TH2 autoimmune hypothesis can well explain the pathophysiology of schizophrenia.

Multiple sclerosis is also a TH2 autoimmune disorder. There are some overlaps between multiple sclerosis and schizophrenia.(Stevens 1988) Histaminergic neurons also play important roles in trigger TH2 autoimmunity of multiple sclerosis. However, the major autoantigen in multiple sclerosis is myelin protein. Thus, the major target of autoimmune cells or antibodies in multiple sclerosis is myelin sheath. Neurons are seldom destroyed. Thus, there are infrequent negative symptoms such as avolition or social withdraw in multiple sclerosis. In addition, myelin sheath is more dominant in optic nerves or spinal cord. Thus, optic nerves or spinal cord are first affected in multiple sclerosis. However, in the final stage of multiple sclerosis, TH2 autoimmune cells can also enter CNS and release serotonin to cause symptom such as hallucination.

Myasthenia gravis is also an autoimmune disease. The main autoantigen of

myasthenia gravis is acetylcholine receptors. In my theory, autoantigens in schizophrenia are also nicotinic or muscarinic acetylcholine receptors. Several papers found that anti-cholinergic receptor antibodies are found in schizophrenia patients.(Mukherjee, Mahadik et al. 1994; Borda, Perez Rivera et al. 2002; Chandley, Miller et al. 2009) However, the specific type of autoantigen in myasthenia gravis is on the neuromuscular junction. On the contrary, the specific type of acetylcholine receptor in schizophrenia is located in CNS. In addition, myasthenia gravis is a TH9(THαβ) dominant autoimmune disorder not like the TH2 dominance in schizophrenia. Thus, schizophrenia and myasthenia gravis are different diseases. Because one is TH2 and the other is THαβ, it is very rare that the two diseases appear in one patient concurrently. This is the mutual antagonism suggested by several papers. It is worth noting that thymusmyoid cells bearing AchR are the sources of autoantigens in myasthenia gravis. Thymoma or thymus hyperplasia is usually found in myasthenia gravis. In a PNAS paper, autoantibodies against thymocytes are also noted in serum of schizophrenia patients.(Luria and Domashneva 1974) Thus, the autoantigen of schizophrenia might also be AchR.

Witebsky's postulates are the standard criteria to decide if a disorder is an autoimmune disease. There are three requirements in Witebsky's postulates: 1. Direct evidence from transfer of pathogenic antibody or T cells 2. Indirect evidence based on reproduction of the autoimmune disease in experimental animal 3. Circumstantial evidence from clinical clues. Actually, schizophrenia fulfils the three criteria. Inflammatory-related genes, β2 microglobulin, CTLA4 are up-regulated in schizophrenia.(Saetre, Emilsson et al. 2007; Teixeira, Reis et al. 2008; Chittiprol, Venkatasubramanian et al. 2009) In the first criteria, increased B cells, IL-4 T cells, eosinophils, and basophils are seen in schizophrenic patients.(Pfeiffer, Iliev et al. 1971; Leonard 2005; Drexhage, Hoogenboezem et al. 2011) TH2 cytokine such as IL-13 level is decreased after effective anti-psychiatric medication in schizophrenia patients.(Pae, Yoon et al. 2006) Anti-brain antibodies, especially IgE antibodies, are found in serum and CSF of schizophrenia patients.(Bock, Weeke et al. 1970; Ramchand, Wei et al. 1994; Yang, Chengappa et al. 1994) Elevated eosinophil cationic protein and eosinophil chemoattractant eotaxin are also noted in schizophrenia.(Hallgren, Venge et al. 1982; Teixeira, Reis et al. 2008) This suggests that schizophrenia is a TH2 dominant immune disease.(Muller, Riedel et al. 2000) In the second criteria, anti-brain antibody transfer into animals such as mice can induce the EEG and behavior change like schizophrenia. In the third criteria, there is a very strong of HLA association with schizophrenia inheritance. This is reported in Nature magazine.(Shi, Levinson et al. 2009; Stefansson, Ophoff et al. 2009) Specific HLA

haplotypes are also linked to schizophrenia incidence. Several TH2 autoimmune diseases such as asthma are linked to the coincidence of schizophrenia. However, TH17 autoimmune diseases such as rheumatoid arthritis are inversely correlated to the incidence of schizophrenia.(Jones, Mowry et al. 2005) The key anti-TH17 IL-1 receptor antagonist is also up-regulated in schizophrenia.(Akiyama 1999) In addition, there is no association with schizophrenia and key TH17 cytokines: IL-1 and TNFα.(Chowdari, Xu et al. 2001; Handoko, Nancarrow et al. 2003; Saiz, Garcia-Portilla et al. 2006) Although there are several reports about up-regulation of IL-6 in schizophrenia, IL-6 is not a solely TH17 cytokine. It is a general cytokine to induce acute phase response in liver during various pathogen infections. Thus, TH17 autoimmunity for schizophrenia is unlikely. Retinoic acid, which can prevent eosinophil apoptosis, is also reported to be related to schizophrenia.(Goodman 1995; Goodman 1998; Ueki, Mahemuti et al. 2008) Retinoic acid responsive transcription factor-RORC is also related to TH2 immunity activation(Putheti, Awasthi et al. 2010). Several pathogens are like to the occurrence of schizophrenia. Among these pathogens, toxoplasma gondii is the strongest link. Toxoplasma parasite mainly induces TH2 dominant immune response. Toxoplasma infection can favor a TH2 biased host environment. Thus, it also suggests schizophrenia is a TH2 dominant autoimmune disorder. In the Northern Hemisphere, persons with schizophrenia are more often born in the months from January to April. In the Southern Hemisphere, persons with schizophrenia are more often born in the months from July to September. This could be due to the lowest maternal vitamin D level in these months during pregnancy.(Kinney, Teixeira et al. 2009) Vitamin D is a strong TH1 activator and effector. Thus, vitamin D will suppress TH2 immunity. This can explain why birth season affects schizophrenia incidence. The TH1 effector cells are down-regulated in schizophrenia.(Freudenreich, Brockman et al. 2010) THαβ(TH9) immunity is also unlikely because of the down-regulation of NK cells and lack of association with IL-10 in schizophrenia.(Abdeljaber, Nair et al. 1994; Sperner-Unterweger, Whitworth et al. 1999; Jun, Pae et al. 2003) The onset of male schizophrenia is from 10 to 25 years old, and the onset of female schizophrenia is from 25 to 35 years old. Schizophrenia will occur after the Treg reduction with the atrophy of thymus during about 10 years old. The later onset of female schizophrenia can be due to the anti-inflammatory effect of estrogen. Estrogen action delays the onset of schizophrenia in female. DiGeorge syndrome is manifested by thymus atrophy. Thus, Treg production is severely lacking in DiGeorge syndrome. The occurrence of schizophrenia is 100 times higher in DiGeorge syndrome. Schizophrenia is related to lower Treg and IL-2 levels.(Achiron, Noy et al. 1994) IL-2 is a cytokine to stimulate regulatory T cells. This implies that schizophrenia is an autoimmune disease. In several clinical studies,

anti-inflammatory drugs such as aspirin and NSAIDs can slow down schizophrenia progression(Akhondzadeh, Tabatabaee et al. 2007; Laan, Grobbee et al. 2010). It also suggests that schizophrenia is an autoimmune disorder.

In addition, many cytokine gene polymorphism is related to the incidence of schizophrenia especially IL-4 and IL-6.(Mittleman, Castellanos et al. 1997) IL-6 is found to be up-regulated in CSF and serum of schizophrenia patients.(Akiyama 1999) In addition, IL-2 is down-regulated in CSF and serum of schizophrenia. IL-6 and STAT3 are also important mediators in TH2 immunity. IL-2 is the main effector of T regulatory cells. Thus, up-regulation of TH2 helper cells and down-regulation of Treg cells can contribute to the occurrence of schizophrenia. Humeral immunity such as complement activation is also reported in schizophrenic patients.(Maes, Delange et al. 1997) Humeral immunity is the manifestation of TH2 immunological pathway.

About the author

Wan-Jiung Hu is a MD PhD. His former name is Wan-Chung Hu. His MD degree was awarded from National Taiwan University. His PhD degree was awarded from Vaccine science track of Department of International Health of Johns Hopkins University. His PhD thesis was using microarray to identify the host immunological pathway after malaria infection. His first first-author paper: “Common and divergent immune response signaling pathways discovered in peripheral blood mononuclear cell gene expression patterns in presymptomatic and clinically apparent malaria” is published in Infection and Immunity in 2006 October. Thus, he first proposed the THαβ immunity which is host immunity against viruses and certain protozoa. A subsequent paper in 2008 called it TH9 immunity. He was trained as a neurology resident in Department of Neurology of Taipei Mackay Memorial Hospital of Taiwan. Currently, he is doing postdoc research in Academia Sinica, Taiwan. His current research topic is cancer immunotherapy. The author would like to publish this manuscript. If journal editors are interested in this paper, please feel free to contact me.

Table 1. Reported schizophrenic-related gene in PBMCs of schizophrenia

Symbol	p-value	Arrow	Fold	Gene Description
Schizophrenia				
HTR1A	0.028	up	1.27	5-hydroxytryptamine (serotonin) receptor 1A
TCF4	0.023	down	1.21	transcription factor 4
PCDHB1	0.004	up	1.12	protocadherin beta 1

Table 2. Immune-related gene up-regulation in PBMCs of schizophrenic patients

Symbol	p-value	Arrow	Fold	Gene Description
Immune				
PVRL2	0.036	up	1.50	poliovirus receptor-related 2 (herpesvirus entry)
GPR162	0.022	up	1.41	G protein-coupled receptor 162
CPN1	0.007	up	1.38	carboxypeptidase N, polypeptide 1
NDUFA4	0.023	down	1.35	NADH dehydrogenase 1 alpha subcomplex, 4
Septin7	0.023	down	1.33	septin 7
TSPAN18	0.020	up	1.30	tetraspanin 18
CLEC1B	0.029	up	1.28	C-type lectin domain family 1, member B
NKX3-1	0.049	up	1.28	NK3 homeobox 1
LY96	0.031	down	1.27	lymphocyte antigen 96
SH3BP5	0.002	down	1.26	SH3-domain binding protein 5 (BTK-associated)
PLEKHB2	0.016	down	1.26	pleckstrin homology domain containing, B 2
TIPRL	0.015	down	1.25	TIP41, TOR signaling pathway regulator-like
RTN1	0.049	up	1.24	reticulon 1
FTK3	0.028	up	1.22	fms-related tyrosine kinase 3
RTN4RL1	0.018	up	1.22	reticulon 4 receptor-like 1
ITGB8	0.012	up	1.22	integrin, beta 8
TOM1L2	0.035	up	1.21	target of myb1-like 2 (chicken)
NLRP1	0.045	up	1.21	NLR family, pyrin domain containing 1
TMIGD2	0.044	up	1.20	transmembrane and immunoglobulin domain 2
LY6G6C	0.005	up	1.20	lymphocyte antigen 6 complex, locus G6C
HCG27	0.017	up	1.20	HLA complex group 27
S100A7A	0.014	up	1.20	S100 calcium binding protein A7A
NCR2	0.027	up	1.19	natural cytotoxicity triggering receptor 2
CLEC11A	0.031	up	1.16	C-type lectin domain family 11, member A
LTK	0.025	up	1.15	leukocyte receptor tyrosine kinase
IVNS1ABP	0.036	down	1.14	influenza virus NS1A binding protein
RORC	0.031	up	1.14	RAR-related orphan receptor C
ITGA5	0.049	up	1.13	integrin, alpha 5
CPN2	0.042	up	1.13	carboxypeptidase N, polypeptide 2
IGSF11	0.022	up	1.10	immunoglobulin superfamily, member 11

Table 3. TH2 related gene up-regulation in PBMCs of schizophrenic patients

Symbol	p-value	Arrow	Fold	Gene Description
TH2				
HDC	0.001	up	1.57	histidine decarboxylase
ALDH1A1	0.002	up	1.52	aldehyde dehydrogenase 1 family, member A1
CPA3	0.044	up	1.36	carboxypeptidase A3 (mast cell)
CXCL5	0.049	down	1.35	chemokine (C-X-C motif) ligand 5
S100A12	0.030	down	1.30	S100 calcium binding protein A12
TPST1	0.050	up	1.33	tyrosylprotein sulfotransferase 1
CCR9	0.020	up	1.30	chemokine (C-C motif) receptor 9
FCER1A	0.005	up	1.30	Fc fragment of IgE, high affinity I, receptor alpha
RCN3	0.014	up	1.29	reticulocalbin 3, EF-hand calcium binding domain
GATA2	0.005	up	1.27	GATA binding protein 2
HTR1A	0.028	up	1.27	5-hydroxytryptamine (serotonin) receptor 1A
ITGA1	0.014	down	1.23	integrin, alpha 1 | pelota homolog
IFNI16	0.024	down	1.22	interferon, gamma-inducible protein 16
IL4	0.011	up	1.20	interleukin 4
SLPI	0.013	down	1.75	secretory leukocyte peptidase inhibitor
PLA2	0.042	up	1.22	phospholipase A2, group IIF
CTSC	0.014	down	1.20	cathepsin C
GPX1	0.008	up	1.16	glutathione peroxidase 1
RBP2	0.007	up	1.16	retinol binding protein 2, cellular
IL22RA1	0.007	up	1.12	interleukin 22 receptor, alpha 1
PGDS	0.025	up	1.11	prostaglandin D2 synthase, hematopoietic

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