Review

Neuropsychiatric Disorders and Their Relations to Host Immunological Pathways

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Neuropsychiatric Disorders and Their Relations to Host Immunological Pathways

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Abstract

Based on the framework of host immunological pathways, we can link immune dysregulation to neuropsychiatric disorders. Using systemic literature reviews, we find out that many psychiatric diseases are closely related to immune dysfunction. Major depressive disorder is related to the overactivity of THαβ immune response. Bipolar disease is related to the biphasic oscillation of THαβ immune and steroid reactions. Manic period is related to steroid reaction, and depressive period is related to THαβ cytokines. Autism disorder is related to up-regulation of innate immunity and down-regulation of adaptive immunity. Obsessive-compulsive disorder and anxiety are related to TH22 immunity. Once we know the immune dysregulations play important roles in the pathophysiology of psychiatric diseases, we can prevent and treat these detrimental disorders better.

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Introduction About Host Immunological Pathways

Eradicable Host Immune Responses

Eradicable immune reactions represent a class of host defenses aimed at the complete elimination of pathogens and are predominantly initiated by follicular helper T (Tfh) cells. These cells are defined by the expression of the chemokine receptor CXCR5 and the secretion of interleukin-21 (IL-21). Tfh cell function is regulated by key transcription factors, particularly BCL6 and STAT5B, which promote B cell activation, antibody production, and immunoglobulin class switching to IgG, primarily within the germinal centers of lymphoid tissues [1,2].

The T helper 1 (TH1) immune pathway is specialized in the clearance of intracellular microorganisms including intracellular bacteria, protozoa, and fungi. This pathway recruits a network of immune effectors, including type 2 myeloid dendritic cells, type 1 innate lymphoid cells (ILC1), M1-polarized macrophages, CD4+ T cells secreting interferon-gamma (IFN-γ), CD8+ cytotoxic T lymphocytes, invariant natural killer T (iNKT1) cells, and B cells producing IgG3 antibodies. IL-12 plays a pivotal role in initiating the TH1 response, particularly through activation of M1 macrophages, which exert antimicrobial effects via lipid peroxidation mechanisms. Notably, this pathway underlies type IV hypersensitivity reactions, also known as delayed-type hypersensitivity [3].

The TH2 immune pathway is designed to combat parasitic infections and is further subdivided into TH2a and TH2b subsets, which target endoparasites (helminths) and ectoparasites (insects), respectively. These responses involve specialized immune cells and distinct cytokine profiles and are associated with type I hypersensitivity reactions, including allergic responses [3].

The TH22 immune response is oriented towards the elimination of extracellular microorganisms including intracellular bacteria, protozoa, and fungi. This pathway is characterized by the involvement of neutrophils, IL-22-secreting CD4+ T cells, iNKT17 cells, and IgG2-producing B cells. Pathogen clearance in this context is facilitated by reactive oxygen species. TH22 activity is primarily associated with type III hypersensitivity reactions, which involve immune complex deposition and inflammation [1].

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The THαβ immune response targets viral and other infectious particles like prions. This pathway mobilizes natural killer (NK) cells, IL-10-producing CD4+ T cells, iNKT10 cells, CD8+ cytotoxic T cells, and IgG1-producing B cells. The THαβ response corresponds to type II hypersensitivity reactions, wherein antibody-dependent cytotoxic mechanisms are activated [4–6].

Tolerable Host Immune Responses

In contrast, tolerable immune responses are orchestrated to manage pathogenic threats while minimizing host tissue damage. These responses are predominantly regulated by CD4+CD25+ regulatory T (Treg) cells, which promote immunoglobulin class switching to IgA. This process is mediated through transforming growth factor-beta (TGF-β) signaling, which activates transcription factors STAT5α and STAT5β, facilitating immune tolerance in mucosal and systemic sites [1].

The TH1-like immune pathway closely resembles the classical TH1 response but incorporates regulatory elements. It includes macrophages, CD4+ T cells secreting both IFN-γ and TGF-β, CD8+ T cells, iNKT1 cells, and IgA1-producing B cells. This pathway also contributes to type IV delayed hypersensitivity but is modulated to avoid excessive inflammation [2].

The TH9 pathway addresses parasitic infections through regulatory eosinophils, basophils, mast cells, IL-9-producing CD4+ T cells, iNKT2 cells, and IgA2-producing B cells. It is linked to type I hypersensitivity reactions, though with a more controlled inflammatory profile [3].

The TH17 immune response is directed against extracellular pathogens and is mediated by neutrophils, IL-17-secreting CD4+ T cells, iNKT17 cells, and IgA2-producing B cells. This pathway corresponds to type III hypersensitivity, involving immune complex-mediated tissue damage [1].

Finally, the TH3 immune pathway responds to infectious particles through the activity of NK cells, CD4+ T cells secreting IL-10 and TGF-β, CD8+ T cells, and IgA1 B cells. This regulatory pathway is associated with type II cytotoxic hypersensitivity but is tempered by anti-inflammatory cytokines [1].

The overall framework of these immunological pathways is illustrated in Figure 1, delineating both eradicable and tolerable host defense mechanisms.

Bipolar Disorders and Major Depressive Disorder and Their Relations to THαβ Immunity

Bipolar disease and major depression are two common mood disorders. Bipolar disease is characterized by repeat episodes of manic and depressive periods. In the other hand, major depressive disorder is only with depressive episodes. These two diseases have detrimental impacts on public health as well as clinical medicine. Especially during the depressive periods, patients with bipolar disorder or major depressive disorder may commit suicide because they think they are useless or severe guilty feelings. The rate of mood disorders is rising and we need to have better prevention and control strategies for bipolar disease and major depression.

In the modern mainstream psychiatry, bipolar disease and major depressive disease are thought to be cognitive dysfunction. They are related to the brain concentration deficits of neurotransmitters like serotonin during the depressive episodes. In addition, manic episodes are treated by lithium salt. Despite of these managements, the efficacy of these medications is still limited. Therefore, there could be a missing piece of the pathogenesis of these two disorders. Immune dysregulation could be the key point of the pathophysiology of these two diseases [7–9].

Autoimmune disorders like systemic lupus erythematosus and Sjogren syndrome have high co-morbidity with mood disorders like major depression. Systemic lupus erythematosus and Sjogren syndrome are type 2 hypersensitivity diseases and are related to THαβ immunological pathway [10]. In fact, neuropsychiatric symptoms are included in the diagnosis criteria of systemic lupus erythematosus. In clinical experiences, there will be induced depressive disorder after type 1 interferon treatment for chronic hepatitis B or chronic hepatitis C virus infection [11–13]. Type 1 interferon signaling is related to major depressive disorder [14–16]. Type 1 interferons including interferon alpha and interferon beta are key initiation cytokines for anti-viral THαβ immune reaction. Type 1 interferons can shut down many cellular gene transcriptions after virus infection to block the

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viral DNA or RNA transcription hijacking our own cells. Type 1 interferons of THαβ immunity can also compete TH2 related neurotransmitter, serotonin, to suppress its function in brain. Type 1 interferons of THαβ immunity can also compete TH17 related neurotransmitter, dopamine, to suppress its function in brain. There is a case report about interferon-α withdrawal induced manic attack [17]. Interleukin-10 is also a key THαβ immunity cytokine. And, its dysregulation with over-expression is also reported in the major depressive disorder [18,19]. There is also an association between interleukin-10 and bipolar disease [20]. Serotonin and dopamine can both induce happiness sensation in our brain.

On the other hand, glucocorticoid administration can sometimes cause manic episodes in patients receiving immunosuppression treatment. Glucocorticoid is the major hormone to suppress adaptive immunity. Glucocorticoid usually produce in the morning daytime to induce euphoria in our daily activity. The inducer of glucocorticoid, ACTH, is the cleaved product of pro-opiomelanocortin (POMC). Besides generating ACTH, POMC can also produce beta-endorphin and met-enkephalin which are intrinsic opioid substances to increase the happiness sensation. Type 1 interferons are usually secreted and function during sleep to clear the possible tumor cells or viral infections in our body. Excessive sleep is usually related to the episodes of depressive mood. In the epidemiologic study, suicide rates are higher in the high latitude nations. These countries have less sunshine of daytime and more dark periods in the nighttime to increase the happening of depressive disorder. These usually happen in winter of high latitude countries and the disease is called seasonal affective disorder (SAD). Therefore, major depression can be due to excessive type 1 interferons related THαβ overactivity, and bipolar disease can be due to alternate patterns of manic episodes (steroids) and depressive episodes (type 1 interferons). Steroid synthesis gene variation is related to depression disorder [21]. Lymphocyte counts are usually lower during manic episodes because of the action of glucocorticoid [22]. In addition, Toll-like receptors TLR3, TLR7, and TLR9 are initiators of THαβ immunity. And, there is report pointing out the correlation of Toll-like receptors and major depressive disorder [23]. This can help to solve the pathogenesis of these mood disorders.

Autism and Its Relation to up-Regulated Innate Immunity and Down-Regulated Adaptive Immunity

Autism is also an important neuropsychiatric disorder. It affects the development of children and causes severe disability. The incidence of autism seems to increase. The detailed pathogenesis is still unknown. These is still no very effective therapeutic agents to treat autism. Immune dysregulation has been reported in autism, and immune dysfunction may play a role in autism pathophysiology [24–26]. Based on epidemiological studies, easy infections in childhood of autism patients are common findings. In fact, the dopamine deficit hypothesis plays a key role in the pathophysiology of autism. The neurotransmitter, dopamine, is very important in brain reward mechanism for children learning and gaining communication skills [27,28]. The relative lack of dopamine is commonly found in autism patients. And, dopamine is also a vital molecule for the function of follicular T helper cells, immune cells to initiate eradicable IgG dominant adaptive immune reactions [29]. If the infection is chronic, then tolerable IgA dominant adaptive immune reactions will be followed. In autism, innate immune response seems over-active and adaptive immune response seems hypo-active [30]. Immunoglobin levels are usually low in autism children [31]. This can be the reason why autism children suffer from easy infection [32]. Glucocorticoid is important in up-regulate innate immunity and it is elevated in autism patients [33,34]. If pregnant mother received glucocorticoid treatment, the children delivered will have higher chance to get autism disorder [35]. Glucocorticoid also affects the hippocampus mediated learning [36]. TH22 and TH17 immune responses are closely related to innate immune reaction. Another report said that interleukin-17 administration during pregnancy also increase the chance of autism in the offspring. TH17 also have components of Treg cells with production of TGF beta cytokine. And, TGF beta is down-regulated in autism patients [37]. And, both IgG and IgA levels are reduced in autism patients [31]. However, pro-inflammatory cytokines including TNF alpha or interleukin-1 as well as

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chemokines CCL2, CCL5, and CXCL9 are usually elevated in autism patients [38,39]. This implies that over-activity of innate immunity and hypo-activity of adaptive immunity in autism.

Obsessive-Compulsive Disorder and Anxiety Which Are Related to TH22 Immunity

Obsessive-compulsive disorder and anxiety are also very common psychiatric diseases. Patients with Obsessive-compulsive disorder repeat to do some behaviors without control. Other anxiety diseases including panic disorder will also let patients anxious due to stress. TH22 is the IgG eradicable adaptive immunity reaction which is triggered by follicular helper T cells. Autoantibodies are detected in patients of obsessive-compulsive disorder or anxiety disorder [40–43]. Follicular helper T cells use dopamine to help to trigger TH22 immunity. Regulatory T cells can shift eradicable immunity to tolerable immunity to down-regulate TH22 immunity. Thus, Treg cells can reduce anxiety type disorders [44,45]. TGF-β is reduced in obsessive-compulsive disorder [46]. There is a study linking obsessive-compulsive disorder and autoimmune skin diseases [47]. Interleukin-22 plays a key role in skin barrier for protecting bacterial infection. TH22 related cytokines including pro-inflammatory cytokines, TNF alpha, IL-6, IL-8, and IL-1, are detected in patients of obsessive-compulsive disorder [48–52]. Dopamine, epinephrine, and norepinephrine are sequential catecholamines. And, these catecholamines are related to the pathogenesis of anxiety disorders. During stress, sympathetic nerve system will be activated. Thus, catecholamines including dopamine, epinephrine, and norepinephrine will be triggered. Sympathetic activity is fear-or-fight reaction. Then, heart rate and blood pressure will increase. Thus, outside stress can induce anxiety symptoms. Toll-like receptors TLR2, TLR4, and TLR5 are the initiators of TH22 immunity. And, a previous research pointed out that TLR5 knockout mice can reduce the symptoms of anxiety [53].

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