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Spotlight on Neuroimmunology: Illustrations from Neurodegenerative Diseases

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ABSTRACT

The immune system plays key roles in the defense of the organism. However, the effects of the immune system are not limited to the immune functions and have impacts beyond the anti-pathogenes role. Indeed, neuroimmunology is a representative field of how the immune system affects non-immune biological and physio-pathological functions. Herein, we have selected a number of neurodegenerative diseases as illustrative examples to put a spotlight on this important field. Importantly, clarifying the links and interactions between the immune system and the nervous system represents key elements for the understanding neurodegenerative diseases since it will lead to new theories about the pathogenesis and the mechanisms underlying the related processes and thus, provide us with new data and novel tools to both describe the related pathways and develop new therapeutic approaches as well as diagnostic approaches and research methodologies based on such new discoveries.

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1. INTRODUCTION

Neuroimmunology, a field that combines both neurosciences and immunology, is a rapidly growing filed, and meetings are organized worldwide to discuss its latest advances, particularly those related to neurovascular and neurodegenerative diseases [1]-[8], showing the importance of this new area and the advances it will have.

For instance, factors such as the loss of blood-brain barrier integrity influence numerous central nervous system (CNS) disorders [9] since it may allow more factors and molecule to go into the CNS which may have an impact on how the immune system influences the nervous system. In addition, blood soluble biomolecules such as adiponectin, an adipocytokine released by the adipose tissue, have important functions within the inflammatory processes which may have a pathophysiological role in neurodegenerative disorders [10]. Divers immunological cells and mediators [11],[12] have been shown to influence the nervous system and vice versa. Furthermore, the important roles of inflammation in initiating tissue damage have been strongly proved through clinical experiments; nevertheless, it is still difficult to explain the continuity of neurodegeneration after the damage has begun in spite of that magnetic resonance imaging (MRI) has shown no new inflammation [5]. Neuroimmunology needs more investigations and more light should be put on the different related aspects, especially for the neurodegenerative diseases in order to elucidate the related pathways and mechanisms both as patho-physiology process and as principles based on which novel therapies can be developed.

2. NEUROIMMUNOLOGY AND NEURODEGENERATIVE DISEASES

Neurodegenerative diseases constitute typical illustrations of the interactions between the nervous system and the immune system. Indeed, neuroimmunology gives divers example about how neuroimmunology could be a key for the medical future of these severe human pathologies. For each studies example, we can observe how the underlying mechanisms are described with a neuroimmunological context.

Among the neurodegenerative diseases, Alzheimer's disease (AD) is a chronic disease characterized by the loose of cognitive functions and neuronal degeneration [13] with an increased prevalence in aging populations [14]. Pharmaceutical companies, government agencies, national AD organizations and scientific research centers are collaborating to find out the best approaches to manage and eventually treat AD [15]. Amyloid-β (Aβ) brain deposits constitute a major factor in AD pathogenesis [16] and both long-term potentiation and synaptic plasticity are affected by the oligomeric amyloid β (oAβ) [13]. It has been indicated that in AD oligomeric amyloid β has the ability to activate microglia and result in neuroinflammatory mechanism via the pro-inflammatory cytokine IL-1β in AD [13]. In addition, more results indicate that AD is caused by elevated Aβ42 fractions in the brain [17]. Risk factors for late onset AD include genetic component such as ε4 allele of Apolipoprotein E (ApoEε4) and variants of the TREM2 gene [14]. Importantly, TREM2 receptor, that has immune function, has been proposed as a potential pharmaceutical target in AD [14]. On the other hand, a set of nonsteroidal anti-inflammatory drugs (NSAIDs) have been able to reduce Aβ42 is divers researches [17]. These show more potential implications of the inflammatory processes within the AD pathogenesis.

For AD patients with peptic ulcers, a reduction in progression of dementia was observed after the eradication of H. pylori [18] showing another potential link between the immune function and the neuro-symptoms, probably mediated by an inflammatory process. Moreover, considering the hypothesis of amyloid cascade for AD, a lot of researches have recently focused on vaccine therapy for this disease through injectable immunization, which has shown therapeutic efficiency in mice, nevertheless, it has shown severe adverse reactions when applied clinically, and it constitutes a challenge that many researchers are working to overcome [19].

Multiple sclerosis (MS) is another autoimmune disease mediated by T cells [20] that targets the CNS myelin via a chain of immune pathway reactions [21]. Yet, although the antibodies roles in MS are not very clarified, many findings support those antibodies have pathobiological roles within the pathogenic processes of MS [22]. Moreover, many immunotherapies exist for MS [21], these therapies are divided based on their targets and pharmacological approaches. The progress made in understanding MS disease mechanisms and new therapies development is highly noticeable mainly thanks to the exploitation of magnetic resonance imaging (MRI) technique capacities [5] as a diagnosis and evaluation tool.

Myasthenia gravis (MG) represents also an autoimmune disease in which proteins of the postsynaptic membrane in the neuromuscular junction are targeted by autoantibodies that the body produces [23]. MG is characterized by fluctuating muscle weakness [24]. This rare disease involves T-cell (Treg) differentiation and NF-κB signaling pathway within the patho-processes [23]. It is also important to study the potential predictive factors associated with such diseases. Recently, a work has been done over a short period of time in Japan to investigate myasthenia gravis disease predictive factors that cause the increased incidence of elevation of the titer of anti-acetylcholine receptor antibodies in patients living in Kanazawa city [25]. It has been found that patients with late-onset myasthenia gravis had a higher incidence of anti-Acetyl choline receptors antibody titer elevation compared to others with early-onset MG, and that thymus removal enabled the prevention of the increase of the antibody titer in patients with non thymoma-related myasthenia gravis [25]. These and other results further highlight the immunological involvement in this neurological disease.

Opsoclonus-myoclonus syndrome (OMS) is a rare paraneoplastic syndrome [26],[27] that represents another illustration of the neuroimmunological interactions. It is characterized by opsoclonus, myoclonus, and ataxia [26],[28] and it has been associated with neuroblastic tumors in children [26]. For this rare disorder with neurological component, it has been suggested that this syndrome could be another manifestation of HIV infection [29] and the implication of B cell mechanisms within the disease pathway [30] point the immunological aspects of this syndromes considered as a neuroinflammatory disorder [31]. Thus, suppose that therapies might be provided by neuroimmunology.

3. DISCUSSION

These examples point out the applications neuroimmunology could have in neurological diseases and illustrate the perspectives that the recent findings would lead to. Therefore, we expect that the data provided by neuroimmunology will not only allow us to map the pathway of some pathological and physiological process, but will also allow us to develop new treatments such as the possible implication and therapeutic use of cytokines, cytokine antagonists, and soluble adhesion molecules in some

neuroinflammatory disorders [30]. On the other hand, promoting the development of tolerogenic dendritic cells by hepatocyte growth factor has been shown to limit mouse autoimmune neuroinflammation [32] which represent a hope for the neuroinflammatory disorders.

Importantly, G protein coupled receptors (GPCRs) that exist and play important functions within both the immune system and nervous system represent an important target within the modern pharmacology [33]-[36] thus, further investigation on the GPCRs [37]-[39] remain important for solving future challenges that will face neuroimmunology especially from a pharmacological perspective [40] including drug design and discovery [41],[42] and drug screening [43],[44].

4. PERSPECTIVES

It is important to develop new techniques and novel approaches [45],[46] with higher sensitivity than those existing at the moment, in order to elucidate more clearly the mechanisms of these neurodegenerative diseases, particularly techniques able to detect the very tiny amounts of immune factors. Indeed, increasing number of evidences is pointing immune factors have been shown to play roles in divers non-immune pathways and non-immune pathways can influence the immune functions (or be linked to) including obesity [47], diabetes [48], nutrition-related [49], schizophrenia [50], brain function [51] and aging-related changes to immunity [52].

5. CONCLUSION

Further investigations involving multidisciplinary approaches remain required to elucidate the key features of the different aspects of the neuroimmunology from divers fields. Such goal can be achieved especially by applying modern methods which would allow as a deeper understanding of the different immune functions and their implications within the neurodegenerative diseases, not only via the inflammatory processes but also through the different cellular and molecular pathways. Importantly, a better understanding of the neuroimmunological concepts within the context of neurodegenerative diseases would surely allow us to improve the current therapeutic approaches via controlling drugs side effects and developing novel treatments.

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