Immunity of Central and Peripheral Nervous System

ABSTRACT

Immune privilege is an absent or limited response of the immune system to antigenic challenge. It seems to be of particular benefit in three organs: the brain, eye and pregnant uterus. Recent data have revealed that the CNS and PNS are not isolated from the immune system. They are in interaction with the peripheral immune system. It is more appropriate to consider the CNS and PNS to be “immune-specialized area”. In this paper we aimed to review the immunity of both central and peripheral nervous system. We will also mention about specific disorders that have been understood more clearly in immune respect and experimental models of immune-mediated neurological diseases.

Key Words: Immunity, central nervous system, peripheral nervous system, immunological models

IMMUNITY OF CENTRAL NERVOUS SYSTEM

Many body sites are recognized for their varying degrees of immune privilege which characterized by an absent or limited response of the immune system to antigenic challenge. Immune privilege seems to be of particular benefit in three organs: the brain, eye and pregnant uterus. An explanation for the existence of this phenomenon is that activation of the immune system could be detrimental for the organism. The immune privilege of the central nervous system (CNS) is indispensable for damage limitation during inflammation. The immune privilege of the brain is certainly not absolute but is relative to other organs. Tissues that are rapidly rejected by the immune system when grafted in sites.
such as the skin, have a prolonged survival when grafted into the CNS. Initially, CNS immune privilege was explained by the following reasons: the isolation of the CNS from the immune system by the blood-brain barrier (BBB), the lack of draining lymphatics, and the apparent immunoincompetence of microglia (the resident CNS macrophage). Recent data have changed this viewpoint by revealing that the CNS is neither isolated, nor passive in its interactions with the immune system. Peripheral immune cells can cross the intact BBB, CNS neurons and glia actively regulate macrophage and lymphocyte responses, and microglia are immunocompetent. It is more appropriate to consider the CNS to be “immune-specialized”, and acknowledge that immunosurveillance of the CNS is a very important component of host defence.

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The endothelial BBB has been considered the point of entree for circulating immune cells into the CNS. The BBB is formed by highly specialized endothelial cells, which inhibit transcellular molecular traffic owing to its low pinocytotic activity, and restrict paracellular diffusion of hydrophilic molecules because of complex interendothelial tight junctions. Leukocyte migration across the BBB is a multi-step process. An initial contact of the circulating leukocyte with the vascular endothelium, generally mediated by adhesion molecules of the selectin family and their respecting carbohydrate ligands. Lymphocytes can also roll via the interaction of alpha-4 integrins with their endothelial ligands VCAM-1 or MAdCAM-1. The rolling leukocyte can perceive chemotactic factors from the family of chemokines, which are presented on the endothelial surface. This leads to the activation of integrin family. Activated integrins are able to mediate the firm adhesion of leukocytes to the vascular endothelium. This process results in leukocyte diapedesis, through inter-endothelial cell junctions or directly through the endothelial cell (Figure 1).

Figure 1. After the first contact between a leukocyte and endothelium (tethering), rolling occurs. The interaction between selectin and selectin ligands play a role in this stage. In the next step activation of the integrins is triggered by the attachment of chemotactic factors to their receptors on the surface of leukocyte (activation). As a result of the interaction between the integrins and the cell adhesion molecules, leukocytes stick to the endothelium (adhesion) and they migrate (transmigration).
In neuroimmunology area, leukocyte recruitment into the brain is an important topic. A better understanding of the regulation of this process might provide clues for treating immune-mediated neurologic diseases like multiple sclerosis (MS). In inflammatory conditions of the CNS, the expression of adhesion molecules and chemokines is induced on BBB endothelium and the choroid plexus epithelium, providing additional traffic signals for circulating leukocytes. Even when the endothelial BBB becomes leaky, T lymphocyte recruitment into the CNS remains tightly controlled. Although leukocyte recruitment is modest and delayed in the brain as oppose to the other organs, brain does exhibit key features of inflammation (such as glial activation, edema, major histocompatibility complex (MHC) expression, synthesis of inflammatory mediators). Much of the key evidence suggest that inflammation and inflammatory mediators contribute to acute, chronic and psychiatric CNS disorders.

Recent studies have demonstrated a strong link between neurodegeneration and chronic inflammation which has been reported in Alzheimer’s disease, Parkinson’s disease and amyotrophic lateral sclerosis. Inflammatory lesions can be induced either by T lymphocytes, by B cells and autoantibodies as well as by cells from the innate immune system. Antibody-mediated autoimmune diseases principally affect peripheral nerves and the neuromuscular junction. It is rare in the CNS because the presence of the intact BBB restricts serum proteins from reaching the CNS in sufficient concentrations to cause disease.

Another key question in understanding communication between the immune system and the brain is: how does the CNS identify the extend of inflammatory or other immune responses occuring in peripheral tissues, so that it may respond appropriately? Although the data has been quite diverse and several mediators and mechanisms have been thought to be responsible for interacting with the CNS, cytokines (especially IL-6) produced during the inflammatory response have been suggested as the important humoral mediators in this process.

In most situations, effector mechanisms involved in the immune response inside the CNS, lead to a protective immunity. But, the final outcome is remarkably influenced by the type of antigen and the local microenvironment. This process may result in the clearance of the pathogen, sometimes associated with a bystander CNS damage. The CNS is not only the site of an effective immune response aimed at eradicating pathogens but can sometimes become the target of aberrant immune reactions against *self-antigens* leading to autoimmunity.

**IMMUNITY OF PERIPHERAL NERVOUS SYSTEM**

The peripheral nervous system (PNS) is separated from the systemic immune compartment by the blood-nerve barrier (BNB), which does limit access of immune cells and soluble mediators into the PNS tissue. Although, the PNS has also been considered an immunologically privileged site, it is not as strictly as the CNS. Soluble factors or cells can easily access the PNS at the root entry and exit zones and at the nerve terminals where no barrier exists. Activated T and B lymphocytes, antigen-presenting cells (APC), like macrophages, Schwann cells contribute to the local immune network. Adaptive and innate immunity are functionally connected allowing for intensive interactions between hematogenic cells and glial elements of the PNS (Figure 2).

Under physiological conditions, a well-balanced network of immuno-competent cells and soluble factors carefully regulates the immune system within the local tissue compartment. The maintenance of self-tolerance is a key requisite in this setting. In autoimmune diseases, self-tolerance breakdown, and autoreactive T and B cells that are part of the normal immune repertoire are released and can initiate organ-specific
damage. Why and how autoreactivity escapes the regulatory mechanisms is still unknown in most immune-mediated neurologic disorders. Immune-mediated inflammatory disorders of the PNS are characterized by cellular infiltration, demyelination and axonal loss in the affected portion of the nerve. However, it remains unidentified how the cascade of autoimmune responses targeting PNS is initiated. One pathogenic mechanism for autoimmune neuropathies is "molecular mimicry". In a proportion of patients diagnosed with Guillain-Barré syndrome (GBS), epitopes shared between the enteropathogen Campylobacter jejuni, cytomegalovirus or Haemophilus influenzae and nerve fibers have been identified as targets for aberrant cross-reactive B cell responses. As it has been mentioned before, there is evidence that B cells are also involved in the pathogenesis of many other immune-mediated neurological disorders, such as paraneoplastic neurological syndromes, myasthenia gravis, Lambert-Eaton myastatic syndrome, anti-voltage gated potassium channel associated neuromyotonia, dermatomyositis, GBS, chronic antibody-associated demyelinating polyneuropathies.

Although it is not an aim of our paper to review information about all immune-mediated neurological disorders, we would like to focus on specific disorders that have been understood more clearly in immune respect.

MYASTENIA GRAVIS

Myasthenia gravis (MG) is a prototypic autoimmune disease that fulfills the strict criteria for an autoantibody-mediated disorder against a known target autoantigen. The autoantigen in MG is the acetylcholine receptor (AChR) at the postsynaptic membrane of the neuromuscular junction (NMJ). Anti-AChR autoantibodies impair neuromuscular transmission by complement-mediated destruction of the NMJ, by increasing AChR turnover following AChR cross-linking and by interference with ion channel function. Antibodies which have been produced in the systemic circulation cross the blood-nerve barrier and with the locally produced antibodies contribute to demyelination and damage to axons. The inflammatory process is terminated by T cell apoptosis, secretion of antiinflammatory cytokines like interleukin-10 (IL-10) and transforming growth factor-β (TGF-β).

Figure 2. Autoreactive T cells (T) in the systemic circulation are activated when a specific autoantigen is presented by antigen presenting cells (APC) and they cross the blood-nerve barrier. Chemokines, cellular adhesion molecules and matrix metalloproteinases play role in this step. T cells in the peripheral nervous system activate macrophages (MF) and phagocytic activity starts. Production of cytokines, secretion of toxic agents like nitric oxide, matrix metalloproteinases and proinflammatory cytokines like tumour necrosis factor-α (TNF-α) or interferon-γ (IFN-γ) occurs. Antibodies which have been produced in the systemic circulation cross the blood-nerve barrier and with the locally produced antibodies contribute to demyelination and damage to axons. The inflammatory process is terminated by T cell apoptosis, secretion of antiinflammatory cytokines like interleukin-10 (IL-10) and transforming growth factor-β (TGF-β).
expression of adhesion molecules and matrix metalloproteinases that are required for BBB and tissue infiltration. Activated T cells recognize the autoantigens within the CNS, initiating an inflammatory response. This process ultimately results to myelin destruction and axonal damage. Locally expressed pro-inflammatory mediators contribute directly to tissue damage and to further destruction of the BBB and chemokine release, which result in subsequent waves of leukocyte infiltration.

Symptoms usually start before age 40 years and most patients have a relapsing course from the onset (relapsing-remitting MS: RRMS). With time, many patients with RRMS develop apparent continued progression that may be independent of symptomatic relapses (secondary progressive MS: SPMS). Essentially, any symptom or sign of CNS origin may be seen in MS. Some of them are common, such as symptoms of optic neuritis, internuclear ophthalmoplegia, sensory symptoms, weakness, ataxia.

NEUROMYELITIS OPTICA

Neuromyelitis optica (NMO) is a devastating disease affecting primarily young woman. The disease principally attacks the optic nerves and the spinal cord causing blindness and paralysis. In recent years, Lennon et al described the presence of serum autoantibody marker, NMO-IgG which is highly specific for NMO. NMO-IgG selectively targets astrocytic end feet at the glia limitans and is directed against the water channel aquaporin-4.

EXPERIMENTAL MODELS OF IMMUNE-MEDIATED NEUROLOGIC DISEASES

EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS

Experimental autoimmune encephalomyelitis (EAE) is a model of the neuroimmune system response, primed with central nervous system (CNS)-restricted antigens. Encephalomyelitis occurs in response to immunization with CNS myelin. Immunization induces a T lymphocyte response against myelin antigens. T cells and other leukocytes enter the CNS by extravasation across the BBB endothelia and basal laminae. Within the CNS, T cells are re-activated by recognition of antigen presented by local and infiltrating antigen-presenting cells. Activated T cells initiate an inflammatory response in the CNS that includes production of cytokines and chemokines which results in myelin damage.

EXPERIMENTAL AUTOIMMUNE NEURITIS

Peripheral nerve inflammation and demyelination is induced by immunization of animals with peripheral myelin proteins such as P0, P2 or galactocerebroside. The target tissue includes both spinal cord roots and axons, but the roots are favored, as in GBS, the human disease which is modeled by this immunization. The pathological hallmark of experimental autoimmune neuritis (EAN) is the infiltration of the PNS by lymphocytes and macrophages, which results in multifocal demyelination of axons predominantly around venules.

EXPERIMENTAL AUTOIMMUNE MYASTENIA GRAVIS

Experimental autoimmune myastenia gravis (EAMG) is induced in susceptible strains of mice by subcutaneous immunization with AChR purified from Torpedo californica (tAChR) emulsified incomplete Freud adjuvant. Susceptible mouse strains exhibit muscle weakness usually after two AChR immunization in Freud adjuvant. Muscle weakness in human MG and EAMG is similar. It must be mentioned that experimental models of immune-mediated neurological diseases are useful for testing specific treatment modalities. But, we should remember the fact that the animal models can not always perfectly represent the human disease and the data from experimental models should be interpreted with caution.

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