

The Role of Mast Cells and Neuroglia in Neuroinfectious Diseases

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Abstract

The central nervous system may be infected by a wide range of microorganisms. However, immune response in the central nervous system is too limited and delayed, and penetration of antimicrobials from blood-brain barrier is also limited. As a result, morbidity and mortality rates of these infectious diseases are still high despite advanced antimicrobial therapies. Many of these infections are life threatening, and an important percentage of individuals who survive may experience severe and permanent neurological deficit. In the last decades, various experimental studies have provided some insight into the molecular and cellular basis of the human neuroinfectious diseases, including the host response to pathogens, pathobiology of neuroinflammation, and mast cell–microglia crosstalk.

In this content, mast cells are multifunctional cells which are known as central players in classic IgE-associated allergic disorders. Actually, they have a critical and protective role in host defense against parasites, bacteria, fungi and viruses in the context of both innate and adaptive immune responses through releasing a wide range of pro-inflammatory and immunoregulatory molecules and their characteristic surface receptors for cytokines and chemokines. In this content, mast cells have an important role in protection against infections of the nervous system, as well. Recent studies show that mast cells form the major link between neurons and inflammation via neuropeptides. Namely, neuropeptides may induce human mast cell degranulation and chemokine production.

This review will provide an overview of the innate and adaptive immune responses, neuroinflammation, the roles of neuroglia and mast cells, and mast cell–glia crosstalk. Development of novel therapies targeting neuroinflammation and an agent which is efficacious in acute and neurogenic inflammation called N-palmitoylethanolamine will also be discussed.

Keywords: CNS; Infection; Mast cell; Neuroglia; Neuroinflammation

Introduction

The central nervous system (CNS) may be infected by a wide range of microorganisms, including bacteria, viruses, fungi and parasites. Although advanced antimicrobial therapies have been developed, these infectious diseases still remain a major cause of morbidity and mortality, and prompt medical attention/intervention is needed. Many of these infections are life threatening and many of the individuals who survive experience severe and permanent neurological deficit. The main factors accounting for the devastating effects of these infections include 1- limited and delayed immune response in the CNS which is attributable to the local deficiency in complement system and immunoglobulins, 2- limited penetration of many antimicrobial agents from blood–CNS barrier, and 3- the unique characteristic of the CNS anatomy [1].

Furthermore, when infectious pathogenic organisms enter the nervous system, they may cause a wide range of clinical syndromes, such as progressive multifocal leukoencephalopathy (PML), chronic meningitis, herpes simplex encephalitis, West Nile virus neurologic infections, Creutzfeldt–Jakob disease, neurosarcoidosis, AIDS–related viral infections of the nervous system, etc. The host response to pathogens differs among individuals depending on the individual's current immune status and efficiency of immune responses. For instance, polyomavirus (JC virus), the etiological agent of PML, infects 50% or more of the adult population throughout the world, however, only a small percentage of infected individuals become complicated with PML, an extraordinarily rare complication of this infection in otherwise normal persons. Although the majority of PML cases occur in severely immunosuppressed individuals, PML has been increasingly diagnosed in patients treated with biological therapies such as monoclonal antibodies (mAbs) that modulate immune system functions [2].

In recent years, researchers have focused on understanding the pathophysiology of neuronal injury associated with neuroinfectious diseases in order to develop new diagnostic markers and therapeutic targets. In this content, various experimental studies have provided some insight into the molecular and cellular basis of the human neuroinfectious diseases, including the host response to pathogens, pathobiology of neuroinflammation, the roles of glial and mast cells (MCs), and mast cell–microglia crosstalk. In the last decades, interactions between nervous system and immune system are also of great interest by many researchers. The investigation of mast cell–glia communication has provided new perspectives for the development of novel therapies targeting neuroinflammation. One of the suggestions as being the basis of novel therapies is modulating activation of non-neuronal cells that normally control neuronal sensitization [3,4].

Furthermore, an important member of the immune system is the mast cell which mainly express critical effector functions in allergy and anaphylaxis. MCs have also been recognized as crucial effectors in both innate and adaptive immune responses. Studies using MC-deficient mice have shown that MCs protect the host against bacteria, fungi, protozoa, and even viruses through releasing proinflammatory and chemotactic mediators. Indeed, a variety of antimicrobial activities of

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MCs have been reported in the literature in the last decades [5].

In response to bacterial infection, MCs increase the recruitment of neutrophils and aid in bacterial clearance. Interestingly, they are capable of phagocytosis, a vital component of the innate immune system, which results in bacterial cell death with lysis of the dead organisms. On the other hand, MCs can modulate the adaptive immune responses and are capable of antigen presentation [6].

In addition, MCs are both sensors and effectors in communication among nervous, vascular, and immune systems. MCs form the major link between neurons and inflammation via neuropeptides. Neuropeptides activate human mast cell degranulation and chemokine production. In this content, the connection between MCs and MC mediators may lead to a better understanding of the neuro-immune-endocrine systems in physiology and pathology. Moreover, widening the knowledge of cytokine network will help us to understand how immune system cells influence the central nervous system [7].

Innate and adaptive immunity

The host response to pathogens has two components, the innate and adaptive responses. The innate system includes anatomical defenses which restrict pathogen invasion, the complement system and myeloid cells that first sense and attack to pathogens. Neutrophils, monocytes, basophils, eosinophils and MCs are cells of myeloid lineage and together with natural killer cells, they are involved in innate immune responses. These cells detect and respond to pathogens within the bloodstream. On the other hand, tissue macrophages which are also of myeloid origin residing within tissues, may be the first to encounter pathogens. These cells release chemotactic signals as a determinant of pathogen activity in that tissue and promote the transition of circulating leukocytes into the area of infected tissue. In fact, innate immunity, by itself, may be insufficient to protect a host against an invading pathogen or to prevent disease from occurring. However, if innate immunity fails, the organism may be detected and attacked by the mechanisms of adaptive immunity.

On the other hand, the adaptive immune responses involve lymphocytes which target to destroy pathogens and their toxic molecules. It is crucial that they attack only in response to molecules that are foreign to the host and not to the molecules of the host itself. The ability to distinguish 'foreign' from 'self' in this way is a fundamental feature of the adaptive immune system. There are two classes of such responses: 1- antibody responses which are carried out by B lymphocytes, 2- cell-mediated immune responses which involve T cells. In antibody responses, B lymphocytes are activated to secrete antibodies, called immunoglobulins. The antibodies circulate in the bloodstream and permeate the other body fluids, where they bind specifically to the foreign antigen that stimulated their production. Antibody binding inactivates viruses and microbial toxins (i.e. tetanus toxin) by blocking their ability to bind to receptors on host cells. Binding of antibody also marks invading pathogens for destruction, primarily by making it easier for phagocytic cells of the innate immune system to ingest them.

Indeed, the innate and adaptive immune responses both function to protect the body against invading organisms, but they differ in a number of ways: (1) The innate immune system is constitutively present and reacts immediately to infection, whereas the adaptive immune response takes some time to develop. (2) The innate immune system is not specific in its response, however, the adaptive immune system is antigen-specific and reacts only with the organism that induced the response. (3) The adaptive immune system exhibits immunological memory, remembers that it has encountered an antigen, and reacts

more rapidly on subsequent exposure to the same organism, whereas the innate immune system does not possess a memory [8-11].

Neuroinflammation

Infection and injury induce a physiologic response called inflammation in order to remove detrimental stimuli and initiate tissue healing. In the central nervous system, this process is termed neuroinflammation. In acute neuroinflammation, microglia become activated and phagocytose dying cells and release pro-inflammatory cytokines, thus they prevent the dissemination of the area of injury [4,12,13].

However, prolonged neuroinflammation causes deleterious effects through activating pro-inflammatory cytokines which results in increased oxidative stress, and neuronal death. The cytokines released by necrotic neurons induce further activation of microglia and astrocytes, resulting in positive feedback loops working independently in which the original pro-inflammatory molecules are no longer needed.

Neuroinflammation is a common mechanism influencing the severity, progression, and complications of neuroinfectious diseases, and is an important candidate target for neuroprotective therapies. For instance, sustained neuroinflammation is implicated in HIV-associated neurocognitive disorder [14,15]. Neuroinflammation is also a key feature in other nervous system pathologies such as neurodegenerative diseases [16], stroke, spinal cord injury [17], chronic pain, and neuropsychiatric disorders such as anxiety, depression and schizophrenia. Furthermore, inflammation in the periphery of the body may impact on central nervous system behaviors, such as cognitive performance.

On the other hand, neuroinflammation may also increase the sensitivity of the brain to stress, thus effecting stress-related neuropsychiatric disorders. And vice versa is also true: namely, stress may stimulate inflammation. Corticotropin-releasing factor (CRF), which is secreted from the hypothalamus under stress, together with neurotensin (NT), can stimulate brain MCs to release inflammatory and neurotoxic mediators that disrupt the blood-brain barrier (BBB), stimulate microglia and cause focal inflammation. As a result, brain MCs may be involved in the pathogenesis of "brain fog," headaches, and autism spectrum disorders (ASDs), which worsen with stress [18,19].

Mast cells

MCs were first described by Paul Ehrlich in 1878 on the basis of their staining characteristics and large cytoplasmic granules, and have long been recognized as key cells of type I immunoglobulin E (IgE)-associated hypersensitivity reactions. Although MCs share similarities with basophil granulocytes in blood, contrasting with basophils, MCs circulate in blood in an immature form as committed precursors until they migrate to a tissue site to settle and complete their differentiation in tissues [10,20].

MCs are present in most tissues in the vicinity of blood vessels, particularly near surfaces exposed to the environment. Thereby, they are distributed in almost all organs and vascularized tissues. They are present in the the gastrointestinal tract, skin, and the respiratory tracts, where they are in close contact with the outside environment. MCs are also normal resident cells of the hair follicles, peritoneum, synovium, and many other organs.

Although they have long been implicated in the pathogenesis of allergic diseases and inflammatory disorders, and well-studied with their protective responses to parasites, their functional role has been found to be more complex than recognized. MCs play key functional roles in distinct nonimmunological activities, such as wound healing following

injury, tissue homeostasis or remodeling, fibrosis, carcinogenesis, and angiogenesis. MCs are found to be critical protagonists in host defence against microorganisms [5,20-24].

Indeed, MCs are effector cells of the innate immune system and are involved in various cell-mediated immune reactions and in infectious diseases as a component of the host reaction to bacteria, parasite, fungi, and even virus infections. This is accomplished through the secretion of cytokines and other soluble mediators. In response to bacterial infection, MCs were found to increase the recruitment of neutrophils and aid in bacterial clearance. Recent studies have shown that MCs can modulate the host's innate immune response to gram negative bacteria by contributing to the process of phagocytosis through the release of pro-inflammatory mediators and presentation of bacterial antigens to T cells [25,26]. MCs have been shown to phagocytose and kill enterobacteria, and are capable of processing bacterial antigens for presentation through class I MHC molecules to T cell hybridomas after phagocytic uptake of live bacteria [27].

MCs have been found to have anti-viral effects, as well. Histamine, protease enzymes and leukotrienes are important mast cell mediators for effective host responses. The cytokines and chemokines produced by MCs in response to pathogens alter the nature of the innate immune response and its effectiveness in eliminating infection. Moreover, vasoactive amines released by MCs in the central nervous system have been proposed to play a facilitating role in the development of the inflammatory response to Sindbis virus [28].

MCs produce a wide range of mediators, including biogenic amines, cytokines enzymes, growth factors [nerve growth factor (NGF)], lipid metabolites, ATP, neuropeptides, nitric oxide, and heparin. There are two different types of mediator release; one is via degranulation which is a very rapid process, the other is the release of de novo formed mediators which results in a longer lasting activation [4,29,30].

Mast cells in the nervous system

As mentioned earlier, MCs are found at host-environment interfaces and in many vascularized tissues in the body [31]. They are also resident in the brain and are localized to the diencephalon and hippocampus and surrounding leptomeninges [32-35]. MCs are found in peripheral tissues innervated by small calibre sensory nerve fibres and within the endoneurial compartment of peripheral nerves, and cerebral blood vessels. During development they enter the brain by way of penetrating blood vessels, with which they remain associated [36].

Specifically, many MCs are found on the brain side of blood vessels adjacent to astrocytic and neuronal processes [35]. MCs are also found on the brain side of the blood-brain barrier (BBB) [37,38]. About 97% of MCs reside on the abluminal (brain) side of the blood vessels, thus, they are able to communicate with neurons, astrocytes, microglia, extracellular matrix, and blood vessels [3].

Under baseline conditions, in the absence of stress, disease, or trauma, the numbers of MCs are considerably smaller than that of neurons, microglia, and other brain-resident cells. Despite their small numbers, activated MCs can impact neurons, BBB, microglia, and astrocytes [3].

Neuroglia

In the host response to pathogens in central nervous system, glial cells are of great importance. Central nervous tissue contains very little extracellular material and consists of a huge number of neurones and their processes embedded in a mass of supportive cells, known as neuroglia. Neuroglia which are highly branched cells occupy the spaces be-

tween neurones and comprise all the non-neural cells of the CNS. The neuroglia have intimate functional relationships with neurones and they provide both mechanical and metabolic support. Four main types of neuroglia are recognised: astrocytes, microglia, oligodendrocytes, and ependymal cells [11,39].

Microglia are small cells, derived from cells of mesenchymal origin which invade the CNS at a late stage of fetal development. In response to tissue damage, microglia transform into large amoeboid phagocytic cells and are thus considered to be the CNS representatives of the macrophage-monocyte defence system. Microglia act as sensors for disturbed brain tissue homeostasis and accumulate locally in response to the invasion of a foreign material in the brain or neuronal injury [3,12].

In addition to being the support cells of the CNS, astrocytes are recognized as active players in the regulation of neural repair, synaptic function, and CNS immunity [14,39,40].

Astrocytes respond to CNS trauma and infection through a complex combination of molecular and cellular events. Astrocytes react to CNS disturbances with enhanced intermediate filament expression, progressive cellular hypertrophy and proliferation [41,42].

Following infection, astrocytes secrete cytokines and chemokines, such as CXC motif ligand 10 (CXCL10), Chemokine ligand 2 (CCL2), interleukin-6 (IL-6), and BAFF, which influence both innate and adaptive immune responses [43]. These responses elicit local CNS immune responses through inflammatory mediators and induce recruitment of additional effector cells of the immune system from the peripheral circulation.

Mast cell- glia interaction

Pro-inflammatory signals released from other non-neuronal cells of immune origin can induce glial cells. In this context, MCs are of particular relevance. Potential interactions between MCs and microglia are based on several molecular mechanisms determined by in vitro experiments [4,44]. For example, activation of P2 receptors on microglia by ATP stimulates the release of IL-33, which binds to mast cell receptors. This event triggers the release of IL-6, IL-13, and monocyte chemoattractant protein 1, which in turn affect microglial activity. Similarly, mast cell tryptase activates microglial protease activated receptor-2 (PAR2), facilitating the release of pro-inflammatory mediators TNF- α , IL-6, both of which subsequently upregulate the expression of PAR2 receptors on microglia (Figure 1). In this content, PAR-2 contributes to neuroprotection and/or neurodegeneration in the brain under pathological conditions. Therefore, PAR-2 has been suggested to be a novel therapeutic target for the treatment of brain disorders.

Moreover, ATP, released from damaged cells is a potent stimulus for microglia in vitro. ATP may act as an autocrine or a paracrine factor for MCs, thus ATP released from one mast cell can provide a rise in Ca^{2+} in the neighbouring cells [4,45-47].

Besides microglia, MCs also have a dynamic relationship with astrocytes. MCs and astrocytes are co-localized in the perivascular and thalamus [48]. In vitro studies show that astrocytes can be activated by MCs via activation of CD40-CD40 ligand interactions, and MCs are also stimulated to release histamine, leukotrienes, and cytokines [49]. Astrocytes also have histamine receptors (H1R and H2R) [50], and cytokines released from astrocytes can induce mast cell degranulation [3,43].

N-palmitoylethanolamine

MCs and glial cells are known to possess endogenous homeostatic molecules, such as N-acylethanolamines. These molecules can be up-

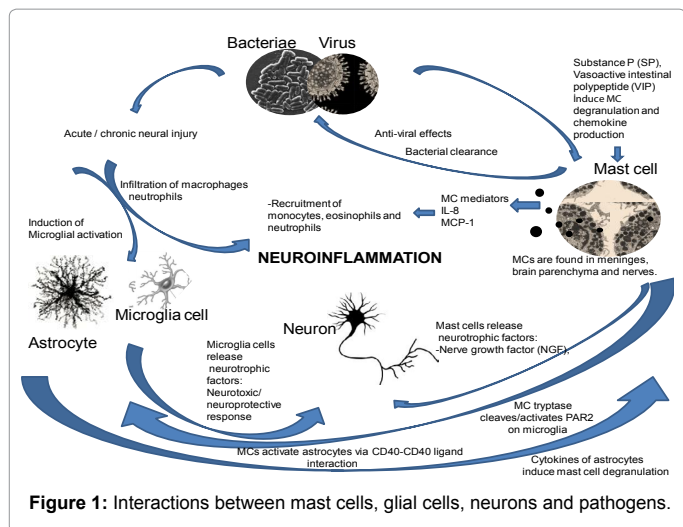


Figure 1: Interactions between mast cells, glial cells, neurons and pathogens.

regulated by the induction of tissue damage or stimulated by inflammatory responses. N-palmitoylethanolamine (PEA) is a member of N-acyl ethanolamines with a key role of maintaining cellular homeostasis when provoked by external stressors such as inflammation. PEA is produced and hydrolyzed by microglia. It downmodulates mast cell activation and, it increases in glutamate-treated neocortical neurons *in vivo* and in injured cortex.

When applied exogenously, PEA has been found to be efficacious in mast cell-mediated experimental models of acute and neurogenic inflammation. It has shown that this fatty acid amide has also neuroprotective effects, proved by a model of spinal cord trauma and a delayed post-glutamate paradigm of excitotoxic death. It was also useful against amyloid β -peptide-induced learning and memory impairment in mice. Thus, inhibiting or modulating the enzymatic breakdown of PEA represents a complementary therapeutic approach to treat neuroinflammation.

Conclusion

Exploring mast cell-mast cell mediator connection and mast cell-glia cell interactions may lead to a better understanding of the neuro-immune-endocrine system functions in both physiologic and pathologic conditions. Understanding the pathophysiology of neuronal injury and the immune response associated with neuroinfectious diseases may further direct us to new therapeutic approaches.

Moreover, targeting endogenous regulators of neuroinflammation may provide a strategy for treating a wide range of nervous system disorders.

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