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FOCUSING ON DEMENTIA: A DISEASE WITH LOSS OF EMOTIONAL AND COGNITIVE ABILITIES

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ABSTRACT

Dementia is a disease of the brain characterized by the progressive loss of cognitive functioning, with memory and thinking impairments, personality changes, and the loss of emotional abilities. Dementia is not a normal part of the ageing process, and the loss of cognitive functioning is severe to the extent that it interferes with daily life. There are several forms of the disease, with Alzheimer's disease (AD), an inflammatory disorder, accounting for most cases. Loss of cognitive and emotional abilities are the striking features of dementia, and these factors combine to produce personality changes that progress to the point that the dementia patient is often unrecognizable as their former self. Symptoms include memory loss, changes in personality, spatial and temporal disorientation, impaired reasoning and judgement, social withdrawal, and difficulty in planning, problem solving, speaking, writing, and performing familiar tasks. Dementia is a major source of morbidity, mortality, and disability, and comes with high economic and societal costs. There is no cure for this disease at the moment, and treatment options are limited. Diagnosis is a multifaceted process that is difficult and expensive, yet early diagnosis is extremely important.

KEYWORDS: *dementia, cognition, behavior, BPSD, neuropsychiatric symptom, neurology, neurodegeneration, brain*

INTRODUCTION

Dementia is the loss of cognitive functioning, with impairments that affect the ability to think, remember, and make decisions, to the extent that it interferes with daily life. Although it usually affects older adults, dementia is not a normal part of the ageing process. The process of the disease progressively damages nerve cells, interfering with normal neural communication, with effects on cognition, behavior, and feelings.

Over the years, improvements in life longevity and population ageing have resulted in the growing incidence of dementia. According to recent estimates, the global number of people suffering with the disease increased by 117% between the years 1990 and 2016 (1), and this number is predicted to increase drastically in coming years (2,3).

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Symptoms that characterize dementia include memory loss that interferes with daily life, changes in personality, spatial and temporal disorientation, impaired reasoning and judgement, social withdrawal, and difficulty in planning, problem-solving, speaking, writing, and performing familiar tasks.

Dementia can take several different forms, including vascular, early-onset, and Lewy Body dementias, although the most prevalent is Alzheimer's disease (AD), which, according to the Alzheimer's Association, afflicts 1 of 9 Americans aged 65 and older (4). The World Health Organization estimates that AD may contribute to 60-70% of dementia cases (5). Additionally, young onset dementia, occurring before the age of 65, may have a prevalence rate of up to 9% of dementia cases (5) and this form can be familial (6). The disease causes morbidity, mortality, and disability and comes with high economic and societal costs.

Currently, there is no cure for dementia, and therapeutic options to slow progression are limited. Symptoms generally become progressively worse over the course of the disease, although some can occur exclusively in the later stages and others may disappear at that point. Demands on family and caretakers increase with disease progression, and as sufferers continue to lose the ability of memory, they may cease to be able to recognize their own family members and friends. There are increasing problems with motor control and diminishing ability to perform daily activities, and behavioral problems such as aggression, all of which cause distress for the person suffering with dementia and additionally, the caretakers and family members who are supporting them.

Dementia can be caused by different diseases, resulting from the loss of neuronal cells and damage to the brain, above and beyond the level of deterioration that occurs with normal biological ageing (5).

AD is the leading cause of dementia, accounting for 60-70% of cases (5). In AD, there is neuronal atrophy and loss of synapses throughout the cerebral cortex, however the etiology is still unknown. The characterizing hallmarks of the disease include the formation of amyloid-β plaques and neurofibrillary tau tangles, with associated neuroinflammation (Fig.1).

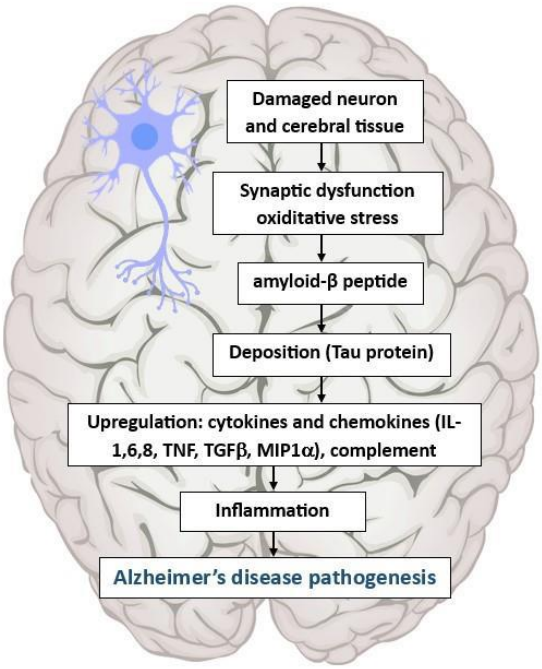

Fig. 1. *Markers of Alzheimer's disease (AD) pathogenesis.*

The predominant theory of AD considers the accumulation, deposition, and ineffective clearance of amyloid-β as central to the development of the disease (7,8). Amyloid-β is phagocytized by microglia and astrocytes which stimulates inflammatory cytokines, leading to neurotoxicity and provoking AD (Fig.2). Growing evidence continues to suggest that these protein aggregates result from a complex interaction of factors.

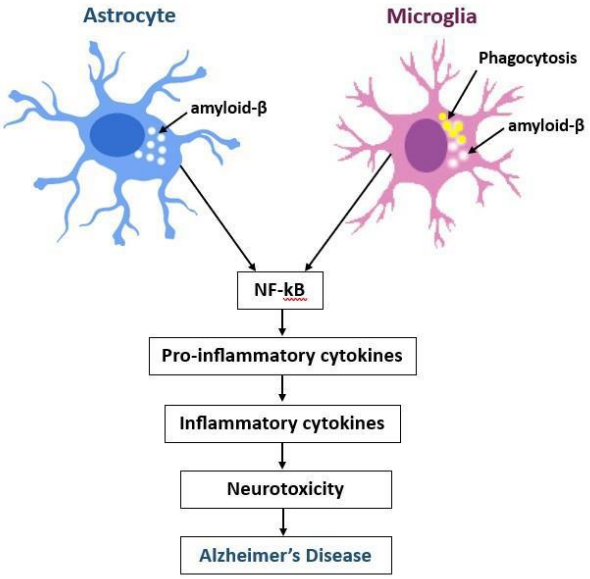

Fig. 2. *Here, we show that astrocytes and microglia affected by amyloid-β generate inflammatory cytokines, which provoke neurotoxicity in Alzheimer's disease (AD).*

In particular, the misfolding, aggregation, and accumulation of proteins is a characteristic event of neurodegenerative diseases, resulting in cellular dysfunction, loss of synaptic connections, and brain damage, and seems to play a role in AD and other forms of dementia (9). Diverse studies have shown that this process is at the base of neurodegenerative pathology, with proteins such as amyloid-β, tau, alpha-synuclein (α-Syn), and TAR DNA-binding protein 43 (TDP-43) implicated in different forms of dementia (10-12).

Recent evidence has shown that protein aggregates can self-propagate their pathological properties utilizing prion transmission with the seeding of protein misfolding, unveiling a new mechanism for the development and progression of neurodegenerative diseases such as dementia (12-14).

The behavioral and cognitive changes of dementia are considered separately, as independent dimensions, although they do influence one another (15). The loss of cognitive and emotional abilities combines to produce profound personality changes along the course of the disease, and in the later stages, the patient is often described by those who know them as being a completely different person, unidentifiable as their former self.

Loss of cognitive abilities

Cognitive impairment increases with the progression of dementia, compromising social, occupational, and daily functioning. The affected domains of cognition include learning, language, memory, executive function, complex attention, perceptual-motor, and social cognition (16). Declines in these domains have significant effects on the independence and performance of daily activities for patients, who often fail to fully realize or acknowledge these cognitive impairments, an occurrence that presents in the early stages of the disease and continues to worsen into the later stages (17).

The level of impairment that precedes dementia is mild cognitive impairment and it presents subtle changes that do not affect an individual's daily functioning. This type of mild deficiency in cognition can be a precursor to dementia, a normal process of ageing, or can arise as a symptom of a treatable, reversible condition, such as depression or acute illness.

Advancing toward moderate cognitive impairment, deficits become more pronounced and widespread, with increasing functional disability that can be seen by the inability to perform more complex tasks. By the later stages of the disease, most cognitive abilities are severely impaired and there is a loss of most normal functioning. Behavioral changes are also frequently observed at the late stages, including aggression, apathy, depression, and agitation (18).

The most prominent cognitive deficit for most varieties of dementia is memory loss, which is often vague. Typically, pronounced deficits concern the areas of new learning and memory recall. Patients have trouble carrying out tasks involving language, executive functions, semantic memory, and visuospatial/constructional skills. AD patients typically have trouble with rapid forgetting and the creation of false or distorted memories (19). Memory impairments in dementia are associated with structural or functional brain integrity, with the disease affecting the structure of neural networks and the formation of memories (20). Memory deficits can be noticed as the first symptoms of dementia, with

the observation of patients' tendencies to repeat themselves, forget quickly, or misplace objects, and may continue to be the dominant symptoms as time, and the disease, progresses.

Social cognition refers to the set of cognitive processes underlying social interactions, such as the effective recognition and use of social cues, the perception of self and others, and knowledge of interpersonal and social norms (21), and is frequently affected and manifested by confusing, abnormal behavior of dementia patients (22).

Dementia types can involve varied categories of cognitive impairment (23). In dementia with Lewy bodies, initial symptoms can involve visuospatial defects, hallucinations, and problems with attention and working memory capacity. Early symptoms in frontotemporal dementia (FTD) are often behavioral or affect social cognition, while those in temporal subtypes can affect language skills. Furthermore, initial symptoms of vascular dementia involve deficits in episodic memory, semantic knowledge, and executive, attention and visuospatial functions (24).

Anosognosia, a condition distinguished by the lack of awareness of a patient's own neurological deficit, is a main behavioral feature of FTD, and patients are often unable to recognize their declining cognitive state (25). However, AD patients show a higher level of recognition of their deficits compared to those with FTD with a relatively similar level of cognitive impairment (26).

Loss of emotional abilities and personality changes

Often, the most painful and difficult aspect of dementia, which affects the patients themselves and additionally, caregivers, is the drastic change in subjective experience and the awareness of self, others, and the external environment that develops with the disease (27). In advanced stages of dementia, the patient changes to such an extent that they are no longer recognizable as the person they once were before the disease, and this comes with great grief and feelings of loss for caretakers.

Emotional abilities are impacted by dementia, with changes in emotional responses and a loss of control over feelings and the ways in which to express them. Some common changes in emotion include irritability, overreaction, rapid changes in mood, and distant or uninterested demeanor.

There is a decline in emotional control and responses, along with changes in social behavior. Those with dementia have trouble communicating their feelings with others and experience difficulty in the social domain regarding empathy and the exchange and processing of shared emotions that is based on the incapacity to apprehend the emotional states of other people (28,29). In particular, FTD is noted for a "decline in social interpersonal conduct" and semantic dementia (SD) is marked by the "loss of sympathy and empathy" (30). Over the course of FTD, there is a gradual degeneration of social dexterity accompanied by diminished self-awareness, and individuals with this disease become socially disinhibited, apathetic, cold, often with notable changes in personality (31-33); new hobbies, aesthetic preferences, or personal views and beliefs may develop that deviate from those before dementia (34).

Self-conscious emotions, such as embarrassment, shame, guilt, and pride, which require a basis of the self in respect to social context, are strongly impaired and this can help to explain the seemingly strange social behavior of those suffering with dementia (35).

Dementia is often accompanied by severe behavioral and psychological symptoms that are non-cognitive. Behavioral and psychological symptoms of dementia (BPSD), the neuropsychiatric symptoms, may affect up to 90% of patients and often occur simultaneously. BPSD can predict poorer outcomes for patients and their caretakers, with increased levels of distress, long-term hospitalization, and overall healthcare costs (36). BPSD includes a wide range of symptoms such as agitation, apathy, depression, psychosis, aggression, and sleep problems. Neurobiological, psychological, and social aspects are all believed to contribute as causes of BPSD symptoms (37).

CONCLUSIONS

Diagnosis of dementia can be challenging, as the initial symptoms can be shared by a number of other conditions, some of which are reversible. These can include thyroid problems, vitamin deficiencies, dehydration and malnutrition, depression, and sensory impairments.

The multifaceted process of diagnosing dementia is difficult and expensive, and can involve the use of cognitive tests, brain scans such as magnetic resonance imaging (MRI) or positron emission tomography (PET), or lumbar puncture to verify the presence of amyloid-β plaques which are present in AD and some other forms of dementia. Early diagnosis is important, but obstacles such as expensive costs and unavailability in certain regions prevent options and availability to all persons. Furthermore, lack of awareness and understanding of dementia can create stigmatization and interfere with proper diagnosis and care (5).

Some medications can help manage the symptoms of this disease. These include antidepressants, anti-anxiety medications and antipsychotics. However, there may often be habituation of the medication or concerning side effects.

To date, there is no cure for dementia and there is no way to slow or stop the progression of the disease, but research is continuing, with the goal of improving diagnosis and treatment. This is of paramount importance since the worldwide prevalence of dementia will only continue to increase in the future, as improvements in health care will continue to expand life longevity and the ageing population will continue to increase.

Conflict of interest

The authors declare that they have no conflict of interest.

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THE AFTERMATH OF ISCHEMIC STROKE: INFLAMMATION, COMORBIDITY, AND DISABILITY

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ABSTRACT

Globally, stroke is the second leading cause of mortality and disability, and the incidence is predicted to rise in the future with the increasing ageing population and a number of young-onset cases. Of the two types of stroke, hemorrhagic and ischemic, ischemic stroke is the most common form and accounts for approximately 87% of cases. It results from the disruption of blood flow to the brain, which occurs with the obstruction of blood vessels; the loss of blood circulation results in the loss of nutrients and oxygen reaching the brain, which leads to the death of neurons and the loss of neurologic function. The characteristics of ischemic stroke include neurologic and systemic inflammation, comorbidity, and severe disability. The initial injury in a stroke can lead to death, and survivors are often left with severe disabilities such as hemiplegia, paralysis or weakness that affects one side of the body. Coexisting medical conditions, such as diabetes mellitus and cardiovascular disease, are essential to stroke. They are usually the cause of the stroke itself, and the severity and type can is associated with long-term outcomes and mortality. Here, we examine these dimensions in ischemic stroke and the ways in which they ultimately predict patient outcomes.

KEYWORDS: *stroke, ischemia, inflammation, comorbidity, disability*

INTRODUCTION

Stroke is the second leading cause of disability and mortality worldwide, with 13.7 million strokes reported globally in 2016 (1, 2), and ischemic stroke accounting for approximately 87% of these (3). The incidence of stroke is expected to increase drastically due to the ageing population and rising number of young people affected in lower and middle-income nations (1).

Ischemic stroke results from the obstruction of blood vessels which supply the brain with blood; the loss of blood circulation prevents oxygen and nutrients from reaching the brain, resulting in the death of neuronal cells and the loss of neurologic function. Stroke can occur from the blockage of arterial circulation, an ischemic stroke, or a burst blood vessel in the brain, a hemorrhagic stroke. Between these two main forms, ischemic stroke is the most common type and a leading neurovascular cause of death and disability (4). Atherosclerosis is the primary cause of ischemia and can cause cerebral thrombosis or embolism.

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Brain ischemia is characterized by neurologic and systemic inflammation, comorbidity, and severe disability. In this paper, we highlight the role of inflammation in ischemic stroke, the related sequela that accompanies and leads to stroke, and the debilitating aftereffects.

Post-stroke inflammation

The loss of blood circulation to the brain that results from ischemic stroke induces a complex chain of biochemical and molecular events, the ischemic cascade, that causes a local neuroinflammatory response and affects systemic immunity (5). There are three general phases of immune response that affect systemic immunity after stroke.

Immediately following the onset of stroke, the peripheral immune system responds to brain injury, which is then followed by a state of immunosuppression with loss of immune cells and responsiveness, increasing susceptibility to stroke-associated infections such as pneumonia (6). Finally, a chronic third phase of sustained low-grade inflammation occurs in the aftermath of a stroke, which is believed to impact the severity of patient outcomes (5).

The initial ischemic injury may produce necrosis of brain cells, while the following ischemic cascade results in further cerebral injury over the course of progressing hours and days (7). Innate immune cells circulating in the brain are engaged at the start of the stroke, followed by the invasion of blood-borne immune cells and the activation of immune cells such as microglia and mast cells residing in the brain (8). Intravascular inflammatory events activate the complement system, which adds to cerebral damage.

Neutrophils are recruited immediately and release metalloproteases (MMP9), elastase, cathepsin G, reactive oxygen and nitrogen species, and the pro-inflammatory cytokine interleukin (IL)-1 (9,10), which mediate inflammation. Peripheral immune cells may enter the brain through the blood-brain barrier (BBB), which opens within hours following ischemic stroke; the choroid plexus and monocytes and neutrophils may also enter through skull-meninges connections such as the leptomeningeal vessels (11,12).

Microglia engage in phagocytosis but are initially activated before the death of neurons, and it appears that microglia involvement has a beneficial effect on limiting post-stroke inflammation (13). On the other hand, microglia activation leads to the release of inflammatory cytokines, which participate in brain damage. Damage-associated molecular patterns (DAMPS) and cytokines generated in the brain in the initial phase of ischemic injury can infiltrate circulation, activating systemic immunity and triggering inflammation (14).

Post-stroke, systemic inflammation can cause acute and chronic complications for patients. With stroke, there is an acute systemic inflammatory reaction and a longer-term low-grade inflammatory response; the combination of these two reactions has been associated with decreased functional outcomes and higher mortality rates in stroke survivors (15). Plasma levels of different inflammatory markers, including the cytokines IL-1, IL-6, and C-reactive protein, have been seen to be elevated in stroke patients (16), and can predict stroke recurrence and functional outcome (17). IL-6 binds to its IL-6 receptors on brain endothelial cells, leading to the increased release of prostaglandin E2 (PGE2), which stimulates the hypothalamus, causing body temperature to rise and producing fever and mediating inflammation (18) (Fig.1).

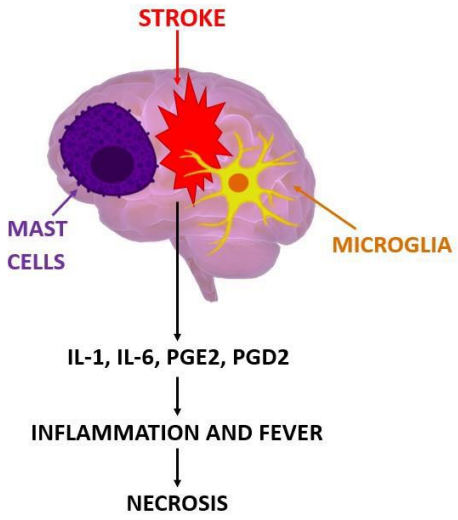

Fig. 1. *Impact of stroke on the brain. Stroke affects brain cells, including microglia and mast cells which secrete inflammatory cytokines after activation, such as IL-1 and IL-6, as well as prostaglandins (PGE2 and PGD2, respectively).*

Much research has begun to focus on the immunological mechanisms underlying stroke, hoping that the modulation of neuroinflammatory pathways could have therapeutic implications (8).

Comorbidity

Comorbidities are a central element of ischemic stroke and are usually the cause of stroke in adults. These comorbidities can be preexisting or post-stroke acquired, with the most frequent being cardiovascular diseases and diabetes mellitus. In fact, the incidence of stroke occurring in the absence of other medical conditions is very low, having been suggested to occur in less than 6% of cases (19,20). Coexisting medical disorders also have great effects on post-stroke outcomes for patients, as they may affect the patient's participation in rehabilitation as well as the efficacy of such treatment.

Medical complications following stroke are common, reported in 40%-96% of patients, and are associated with poor outcomes (21-23) and negative implications for rehabilitation. In one study, stroke severity, atrial fibrillation, and the comorbidity of coronary artery disease and diabetes were associated with disadvantageous outcomes (24). Another study showed a negative correlation between functional outcomes at discharge and mortality rates and the severity and number of coexisting medical conditions in post-stroke patients (25). Frequent comorbid conditions in stroke include hypertension, hypertensive cardiovascular disease, coronary heart disease, diabetes mellitus, obesity, tumor, arthritis, and cardiovascular diseases (24,26). Cardiovascular diseases frequently occur as comorbidity and were seen to affect 40% of post-stroke patients during inpatient rehabilitation (27). However, some stroke-related comorbidities can be modifiable such as atherosclerosis, diabetes mellitus, infections, and certain cardiovascular diseases. For example, hypertension is the most prevalent comorbidity for stroke patients and is a modifiable risk factor.

Furthermore, the inflammatory response occurring after ischemic stroke causes immunodepression associated with post-stroke infections (6). Combined with coexisting medical disorders, modifiable and non-modifiable risk factors influence the mortality rates of stroke patients (28).

Post-stroke disability

Stroke is a leading cause of death, and survival is often accompanied by severe chronic disabilities (29). Additionally, functional deficits following stroke are associated with readmission in hospital, mortality, and early death (30). Disability following ischemic stroke affects between 24%-54% of survivors (31). The burden of disability is more drastic in low and middle-income nations, where regional medical services and rehabilitative care may be lacking, and environmental factors may increase the incidence and severity of post-stroke disability (32).

The location and severity of brain damage predicts the long-term effects produced after stroke, and other factors that influence disability include age of patient at stroke onset, neurological and cognitive deficits, depression, and social support (32). About 70-80% of patients who survive stroke will have disabilities that require rehabilitation and long-term care (33). Data from an Australian study has shown that just over one-third of stroke survivors suffered from a disability that affected their daily functioning, and that of these, 12% needed residential care (34).

Disabilities vary, but frequently there can be changes in speech, learning, and cognition, and hemiplegia, paralysis or weakness that affects one side of the body. Furthermore, stroke may also produce permanent loss of function. Hemiplegia produces diverse complications with motor, cognitive, perceptive, and sensory abnormalities, in addition to visual and language complications (35). The rate of upper-limb disorders is very high post-stroke, with 85% of patients affected in the acute stage, with the frequency dropping to 55-75% after 3 to 6 months from stroke (36,37). Patients often have a deterioration in motor skills that can affect grip strength, causing problems with holding onto objects and the ability to perform a variety of tasks (38). This impairment can greatly reduce patients' self-care and socialization abilities.

Permanent disability interferes with the everyday functioning of patients, affecting their ability to care for themselves and participate in social activities, which ultimately leads to a significantly reduced health-related quality of life (39,40). Post-stroke depression is another prevalent disorder affecting survivors, with studies showing a prevalence rate in between 18%-61% of post-stroke patients (41,42). Depression after stroke has also been related to functional disability, affecting cognition, balance, walking ability, and patient independence (43,44).

Early treatment and rehabilitation are vital to reduce the impact of disability and can improve recovery and patient outcomes and reduce overall healthcare needs.

CONCLUSIONS

Cerebral stroke is a leading cause of death and disability in the modern world, and the incidence is expected to rise drastically over the next decades. Three key features characterize ischemic stroke: neurologic and systemic inflammation, comorbidity, and disability.

Ischemic stroke occurs when there is a disruption in blood circulation in the brain, which results in brain damage with severe consequences. In stroke, the interruption of blood circulation can lead to death or the loss of neurologic function, and survivors are often left with serious chronic disabilities that affect daily functioning and quality of life. These disabilities can include changes in speech, learning, and cognition, and hemiplegia. After the initial ischemic injury, an inflammatory cascade proceeds that results in neuroinflammation and affects systemic immunity. These inflammatory events create a higher rate of susceptibility to stroke-associated infections and may ultimately impact the severity of patient outcome.

Another characterizing feature of ischemic stroke is comorbidity, which is often the initial cause of stroke and an aggravating factor in rehabilitation and recovery. Furthermore, the severity and number of coexisting medical conditions in post-stroke patients have been associated with long-term outcomes and mortality rates. Comorbidities vary, with cardiovascular disease and diabetes mellitus being the most prominent and frequent.

Stroke is responsible for a high level of mortality and produces debilitating consequences in its aftermath. Recently, the immunological mechanisms underlying stroke have emerged as a course of study with the hope that they could be of therapeutic value. Further research is necessary to provide further insight into the mechanisms of stroke and to develop new treatments.

Conflict of interest

The author declares that they have no conflict of interest.

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MENINGITIS: AN OLD DISEASE THAT STILL PERSISTS TODAY. NEW IMMUNE AND INFLAMMATORY ASPECTS

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ABSTRACT

Neuroinflammation is the brain's natural response mechanism to fight off potential threats and encompasses a variety of neurological diseases including meningitis. Meningitis is a serious infectious disease and devastating condition associated with high morbidity and mortality. A common method of diagnosing bacterial meningeal infection is through cerebrospinal fluid analysis. Meningococcal Neisseria (MN) menigitis is one of the most common bacterial infection affecting the central nervous system (CNS), and is characterized by infection of the arachnoid and subarachnoid spaces. The meningococcus binds to the Toll-like receptor (TLR), triggering an immune response and attracting phagocytes in the brain and systemically throughout the body. Activated immune cells produce pro-inflammatory cytokines that aggravate the disease state by destroying brain tissue, including neurons. In infection, activation of the complement system also participates in neurological damage.Therapeutic experiences against meningitis indicate that steroidal anti-inflammatory drugs, such as cortisone and other inflammatory inhibitors, reduce the meningeal pathological state. Blocking inflammation by inhibiting inflammatory cytokines could also represent a new therapeutic strategy in bacterial meningitis.

KEYWORDS: *meningitis, meningococcus, Gram-negative bacteria, immunity, inflammation, Neisseria meningitidis*

INTRODUCTION

Meningitis is a disease that has stably affected man for over 50 years. Traces of meningitis date back to 1500 BC, but the first description was given in the early 1800s (1, 2), while meningococcus, the Gram-negative bacterium responsible for the disease, was first isolated in 1887 (3).

Meningitis is an infection of the meninges that can be caused by several biological microorganisms including bacteria, viruses, and fungi, or by parasites (4). This neurological disease can be very serious and can lead to death even in hours after infection. It can cause permanent damage and 10% of those who contract it will die (5). Other bacteria such as Streptococcus pneumoniae and Haemophilus, and viruses such as herpesvirus, enterovirus, and influenza virus, can also cause meningitis (6). Immunosuppressed subjects are more prone to meningitis due to fungi (7).

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Meningococcal meningitis type B is caused by the bacterium Neisseria meningitidis (NM) which is transmitted by secretions or by physical contact (8). Children, including newborns, and the elderly are at the highest risk for meningitis (9,10). The NM bacterium that causes the disease in humans is made up of different groups: A, B, C, Y, W135, and X (which is less present) (11,12). In Western countries, the most frequent groups are B and C (13). Meningococcal meningitis is one of the most studied and most frequent brain diseases in the African continent, in the United States, and in Europe. For about 50 years, rates of meningococcal disease in Western countries remained approximately the same, at about 1 case per 100,000 people per year (14).

DISCUSSION

The infection occurs mainly in winter and generally affects children who do not yet have their antibody system activated, but adults up to 65 years of age can also be affected. Meningococcus is a Gram-negative bacterium that causes meningitis with usually severe symptoms including headache, shock, nausea, disseminated intravascular coagulation, vomiting, photophobia, lethargy, rash, and multiple organ failure.

NM infection can affect the membranes of the brain and can infect the entire body (septicemia), including the spinal cord, by traveling in the bloodstream (15). Diagnosis should be made based on symptoms such as headache, vomiting, high fever, confusion, fatigue, sensitivity to light, and neck stiffness. In the most severe forms of septicemia, the patient may show organ damage and skin rash. Timely diagnosis and appropriate antibiotic treatment can save the life of the patient suffering from meningitis.

Severe meningococcal infection can affect the central nervous system (CNS) with brain damage and deafness and can cause scarring and even the loss of limbs (16). The infection can also be transmitted by healthy carriers. In addition to those already described above, symptoms of meningococcal meningitis include drowsiness, sudden high fever, and loss of appetite. Protection against the NM bacterium is obtained through vaccination of the patient by age and condition-appropriate doses. Meningitis vaccination can be done with various vaccines such as meningococcal type B vaccine, meningococcal quadrivalent vaccine ACWY, and meningococcal type C vaccine.

The bacterial infection affects the liquid that resides in the ventricles of the brain, causing inflammation, which is a protective response due to the phagocytes which are involved in the immune response. Meningococcus activates both innate and adaptive immunity, which should lead to the improvement of the disease (17). Therefore, meningitis infection causes inflammation of the meninges and brain parenchyma, resulting in meningoencephalitis (18). The infection can vary and affect different brain regions. Encephalitis is inflammation of the brain parenchyma that causes mental disorders and neurological dysfunction, while meningoencephalitis is the inflammation of the CNS involving both the meninges and the parenchyma (19).

In addition to bacteria and viruses, fungi, protozoa, and helminths can also cause meningitis. Bacterial meningitis causes damage to the cerebrospinal fluid and the CNS, resulting in a serious disease that can be fatal. The most common transmissible pathogen that causes the disease is Streptococcus pneumoniae, accounting for 70% of cases, along with NM and Listeria monocytogenes as other common pathogens (20,21). Pneumococcal meningitis and listeria are the most common forms of infection with a mortality rate of up to 20%, although these death rates have been dramatically lowered with vaccinations (22). The encephalitis that occurs in meningitis improves markedly after treatments with anti-inflammatories such as cortisone which reduces the rate of morbidity and mortality (23). However, this treatment is not enough, and new therapies are needed for better results.

The innate immune response participates in the elimination of pathogens and the complement system plays an important role in this reaction. In fact, complement plays a key role in the pathogenesis of neurological disease and, particularly, anaphylatoxin causes cerebral and blood pathological effects (24,25).

In bacterial meningitis, activation of the classic complement pathway begins with the binding of C1q to immune complexes formed by IgM and pneumococcal C polysaccharide (26). The alternative complement pathway occurs when C3b binds to the bacterium, setting off a chain reaction that magnifies complement activation (26). C3b opsonizes the bacterium by facilitating phagocytosis by neutrophils and macrophages, a reaction that causes the secretion of IL-1 and other monokines. Neutrophil phagocytosis of meningococcus is associated with the release of free oxygen radicals (ROS) and lysosomal proteases that cause vascular damage with increased vascular permeability, hemorrhage, and thrombosis (27). Activation of the complement system produces anaphylatoxins C3a and C5a which, by binding to their respective receptors on immune cells, participate in and amplify the inflammatory response (26). The increase in permeability exerted by the complement causes the accumulation of neutrophil granulocytes with an increase in inflammation.

Complement inhibition in bacterial meningitis drastically reduces the inflammatory reaction of the CNS which is one of the main harmful effects (28). The C5a component is the most damaging in bacterial meningitis and targeting

anaphylatoxin C5a production, together with treatment with antibiotics and cortisone, is a very useful therapy (26). Neutrophils migrate to the site where bacterial multiplication occurs and participate in vascular damage. The meningococcus releases C5a-inducing endotoxin and proinflammatory cytokines such as IL-1 and tumor necrosis factor (TNF) (29).

In the disease, there is an inflammatory reaction that affects the subarachnoid space and cerebral parenchymal vessels, contributing to brain damage. In infants, the disease can lead to cerebral palsy with cognitive impairment, blindness, deafness, seizures, and hydrocephalus (30).

The bacterium crosses the blood-brain barrier (BBB) and binds to the Toll-like receptor (TLR) of antigen-presenting cells that are important mediators for the initiation of the immune reaction, triggering an inflammatory response with activation of the NF-kB or protein kinase pathway (31). This leads to the activation of leukocytes which produce immune and inflammatory mediators that damage neurons (32). The cytokines and chemokines produced in these reactions, that are activated by the NM bacterium, attract neutrophil granulocytes which produce large amounts of superoxide anion and nitric oxide, leading to oxidative stress. The resulting mitochondrial damage causes energy insufficiency and cell death, lipid peroxidation, and the breakdown of the BBB. The receptors of the microglial cells activated by the meningococcus increase the phagocytic capacity but can also damage the entire brain, including neurons (33). Microglia and macrophages of the meninges have different types of TLRs that trigger local and systemic immune responses (Fig.1). Microglia are protective cells of the brain and spinal cord that are responsible for defending brain tissue from bacterial invasion including meningococcus. Activation of TLR types 1, 2, and 4 enhances bacterial phagocytosis, whereas activation of TLR9 can cause brain tissue injury through the production of TNF and nitric oxide (NO) (34).

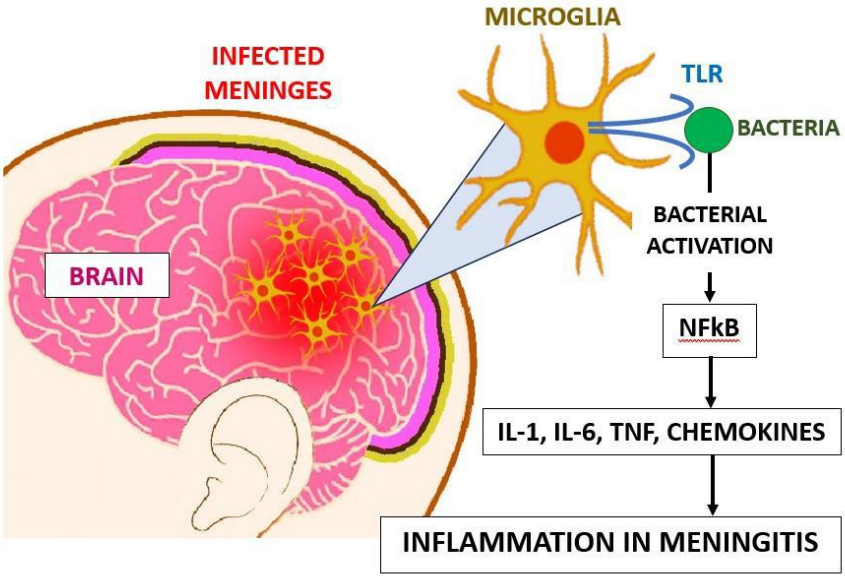

Fig. 1. *The inflammatory response in meningitis. In infected meninges, the bacterium meningitis binds to the Toll-like receptor (TLR) of microglial cells and activates the NF-kB pathway. This leads to the release of inflammatory mediators including IL-1, IL-6, tumor necrosis factor (TNF), and chemokines, resulting in inflammation which is damaging to the brain.*

CONCLUSIONS

Meningitis is caused by various biological agents, including bacteria, viruses, parasites, and fungi. Meningococcal bacterial meningitis, which we have dealt with in this paper, is a severe acute infectious disease of the CNS that causes global morbidity and mortality. The bacterium binds to the TLRs of the antigen-presenting cells and triggers the immune response. In addition, the activation of the complement system by the bacteria can also participate in brain damage. The participation of immune cells, such as macrophages, neutrophils, and lymphocytes, in the infection results in NF-KB activation, leading to the release of pro-inflammatory cytokines which cause neuronal and brain damage. The inhibition of these inflammatory products could represent a valid therapeutic mechanism for treating bacterial meningitis.

Conflict of interest

The author declares that they have no conflict of interest.

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THE RESPONSE OF IMMUNE SENTINELS CAUSING INFLAMMATION IN GLIOMA AND GLIOBLASTOMA

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ABSTRACT

Glioma is a type of central nervous system (CNS) tumor originating in glial cells. Glioblastoma, the most severe form of glioma, is the most common and malignant form of glial tumors. Astrocytoma, which takes its name for having star-like cells, also belongs to this group of glial tumors and is distinguished in various forms. Gliomas are tumors of various types and of unknown etiology and are difficult to cure. The tumor microenvironment is made up of stromal cells, normal fibroblasts, epithelial cells, and T cells. In these tumors, immune cells invade the tumor tissue and may play an important role in prognosis and therapy. Microglia, which constitute about 20% of the total glial cell population, are macrophage-like cells of innate immunity and express CD11b, CD68, and CD163, amongst other markers. Microglia are activated in gliomas and glioblastomas and produce pro-inflammatory molecules, such as the chemokines CCL2 and CCL5, which attract immune cells. The chemokine CXCL8 attracts neutrophils, while CXCL12 is implicated in glioma post-radiotherapy resistance. Pro-inflammatory cytokines such as IL-1, tumor necrosis factor (TNF), and IL-6 are also produced in the tumor environment. In this article we highlight the importance of immune cells in gliomas and glioblastomas, and the role of pro-inflammatory chemokines and cytokines.

KEYWORDS: *glioblastoma, glioma, astrocytoma, CNS, inflammation, tumor, cytokine, chemokine, immunity*

INTRODUCTION

Primary brain tumors are those that arise directly in or near the brain, and secondary brain tumors are the result of metastases from a tumor originating elsewhere. The glial cells, which includes astrocytes, oligodendrocytes, ependymal cells, and Schwann cells, perform the following biological functions: support of the pyrenophores, participation in the myelination of nerve fibers, isolation function towards neurons and nerve fibers, injury repair, trophic functions, and indirect participation in the transmission of the nerve impulse. Gliomas are very common tumors of the central nervous system (CNS) (1,2). There are several types of gliomas that affect the brain and marrow. The most serious is glioblastoma which has a high growth rate and severity, with a median survival rate of approximately 15 months (3). The presence and type of glioma in the CNS and spinal cord is detected with specific laboratory tests.

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Glioma derives from glial cells which act as support and nutrition for neuronal cells and form the CNS together with blood vessels, and gliomas are classified based on the presupposed cell of origin (4). Gliomas are divided into astrocytoma, involving astrocytes, oligodendrogliomas, involving oligodendrocytes, ependymomas, affecting the ependymal cells, and mixed gliomas, affecting both oligodendrocytes and astrocytes (5). In addition, brain tumors can be classified according to growth rate, infiltration, and metastasis capacity, and range from I to IV, where III and IV are more severe and with rapid growth, while tumor cells I and II are with a low and localized growth index (6).

The causes of the onset of gliomas are still obscure, even if they are often attributed to a genetic mutation of unknown origin (7). Exposure to ionizing radiation is also an environmental risk factor (8,9). The study of tumor tissue through genome sequencing can highlight new mutations that may take part in the pathogenesis of cancer. Mutations are diagnosed through analysis of cancer DNA in both brain fluid and peripheral blood, as well as liquid biopsies (10,11).

Even though glioma and glioblastoma look similar, there are differences between them; glioma is the general term to describe a primary tumor of the CNS, while glioblastoma, which is also called glioblastoma multiforme (GBM), is the most malignant and most common tumor of the glial neoplasms, accounting for almost 60% of cases (12). Astrocytoma, which also includes glioblastomas, is the most common type of glioma which affects the brain and, at times, the spinal cord as well. There are various types of astrocytoma including diffuse astrocytoma, diffuse wild type non-mutated astrocytoma, gemistocytic astrocytoma, anaplastic astrocytoma, and anaplastic wild type non-mutated astrocytoma. Glioblastomas also exist in various types such as glioblastoma multiforme, primary wild-type non-mutated glioblastoma, giant cell glioblastoma, gliosarcoma, epithelioid glioblastoma, and secondary mutated glioblastoma multiforme.

Gliomas are brain tumors of unknown etiology and are difficult to cure. Diffuse midline glioma (DMG) develops more frequently near the brain stem, concentrating around the pons and sometimes also invading the cerebellum and hypothalamus (13). GBM shows a genetic heterogeneity that prevents a clear diagnosis, as well as an effective therapy, while in DMG, the most evident mutations can be highlighted, facilitating diagnosis and therapy. The therapy for DMG involves radiotherapy and chemotherapy which can give the patient only transient relief with an extension of survival by only a few months (14,15).

DISCUSSION

The blood-brain barrier (BBB) hinders anticancer therapies in patients with brain cancer, demonstrating that its functionality is not impaired by the tumor (16). In recent times, research has focused on immune cells that invade the tumor microenvironment. For example, T cells, although with low infiltration into the tumor site, can play an important role in both prognosis and therapy (17). T cells that contact activated astrocytes or glioma cells in brain tumors exhibit TCR-CD3 for antigen recognition and T lymphocyte activation (18). The tumor microenvironment consists of stromal cells, normal fibroblasts, epithelial cells, and immune cells (19). The latter influences tumor development by the production of growth factors, cytokines, and chemokines. CD8+ cytotoxic T lymphocytes and Treg regulatory cells play a key role in tumor dynamics (20). Cytotoxic lymphocytes oppose tumor pathogenesis and are present, albeit too few, in greater numbers than CD4+ T helper cells (21). The greater the number of infiltrated CD8+ T cells, the longer the patient's survival is, demonstrating that the immune response at the tumor site is important for survival (22). T lymphocytes help fight the tumor but are also cells that provoke inflammation in the brain, causing negative effects for the patient. However, some gliomas, such as DMG, have much less T-cell infiltration than others (15). Gliomas often show increased expression of growth factor mRNA (TGF-ß1), as well as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) (23). The natural killer (NK) cells of the innate immune system, which we know are responsible for killing tumor cells, are drastically suppressed at glial tumor sites (24,25). While the lymphocyte response in glial tumors is inhibited, the gene expression of inflammatory cytokines and chemokines generated by lymphocytes and macrophages is increased, explaining the cerebral inflammatory state (26).

Microglia distributed in the brain and spinal cord are sentinels of the CNS and defend the brain from damaged cells and infectious agents. Microglia, which comprise up to 20% of the total glial cell population (27), are also part of the innate immune system and represent a collection of primary brain macrophage-like cells expressing CD11b, CD68, and CD163, and other specific markers which have recently been highlighted (28,29). These cells are activated in cerebral gliomas and produce pro-inflammatory molecules, such as cytokines and chemokines, which makes them protagonists in the cerebral inflammatory system.

Macrophages are divided into anti-tumor M1 and pro-tumor M2 categories. In gliomas, they appear to play a part in the immunosuppression due to the increased level of M2 cells and decreased expression of TGF-β1 and TNF (30), while some cytokines such as macrophage colony stimulating factor (CSF) and chemokines attract monocytes to the tumor site (31). In addition, some cells of these tumors express the chemokine ligand CCL2 [also called monocyte chemoattractant

protein (MCP)-1] and CCL5 (32,33). CCL2 mediates the inflammatory process by recruiting macrophages and pro-inflammatory lymphocytes, causing immunosuppression, and it appears that the higher the level of CCL2 is, the more aggressive the tumor is (34).

In gliomas, CCL5 is also involved in inflammation, where it is overexpressed causing the recruitment of macrophages, granulocytic cells, and T lymphocytes (35). The pro-inflammatory chemokine CCL5 is expressed by both glioma and stromal cells and contributes to the migration and proliferation of microglia cells (33). Inhibition of this chemokine appears to reduce the migration of pro-tumor M2 monocytes (36).

Another chemokine of the CXC family, CXCL12, is implicated in the post-radiation therapy resistance of glioma (37). CXCL12 attracts tumor hypotoxic areas to molecules that play a large role in tumor development (38). CXCL8, or IL-8, is a chemokine involved in the recruitment of neutrophil granulocytes, which participates in cell invasion and angiogenesis. The CXCR2 receptor antagonist causes a reduction in glioma expansion, improving patient survival (39).

Astrocytes, taking their name from resemblance to a star, are cells located in the CNS that make-up neuroglia and are divided into fibrous astrocytes that are found in white matter, and protoplasmic astrocytes located in gray matter and form the neurovascular unit. Astrocytes are activated by inflammatory stimuli, leading to modification of their phenotype and overexpression of some proteins including cytokines and chemokines (40). Proteins expressed by astrocyte activation participate in various pathophysiological processes such as cell proliferation, neural growth, motility, autophagy, synaptic plasticity, myelination, immune defense, and BBB formation (41). Astrocytes communicate with each other through cyclic-AMP and following the loss of ATP, the damaged cells activate the P2 receptors of astrocytes, an effect that leads to their modification. In these reactions, the release of proteins stimulates cytokine receptors on astrocytes (42).

Glial-mediated inflammatory immunoreactivity occurs in glial tumors and brain lesions. Gliomas are brain tumors with cells that originate from neuronal stem cells, progenitors of oligodendrocytes, astrocytes, or differentiated neurons. However, since glioma cells and normal astrocytes reside in the same sites, their cell morphology appears similar. In gliomas and other brain pathologies, glia-mediated inflammation involves astrocytes with responsive morphological changes and blood cell recruitment, including immune cells (43). *In vivo*-activated astrocytes can release chemokines into the parenchyma and blood, exerting a recruitment effect for other inflammatory cells. In *in vitro* experiments, astrocytes can be activated to release cytokines by various pathogens, including the bacterial product lipopolysaccharide (LPS) which causes the secretion of various chemokines such as CCL2 (MCP-1), CCL3 (MIP-1α), CCL5 (RANTES), CXCL1, and CXCL2 (44). In addition, tumor necrosis factor (TNF)-treated astrocytes in vitro release other chemokines such as CCL2, CCL5, and CXCL8 (IL-8) (45), demonstrating that these cells are true mediators of brain inflammation.

CONCLUSIONS

In conclusion, even if the immune reaction in glioma and glioblastoma is low, it causes the secretion of cytokines and chemokines which mediate the inflammatory reaction.

Conflict of interest

The author declares that they have no conflict of interest.

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AUTISM SPECTRUM DISORDERS (ASDs): NEW RESEARCH AND POSSIBLE NOVEL THERAPIES

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ABSTRACT

Autism spectrum disorder (ASD) encompasses a collection of brain disorders involving neurodevelopmental and functional disabilities of the brain. It is a disorder of unknown pathogenesis, begins in childhood, and can have different degrees of severity. Additionally, there has been a high incidence of ASD in the last 10 years. The blood-brain barrier (BBB) protects the brain, however in children it is not yet formed, and for subjects with ASD, this allows the passage of harmful inflammatory substances that could be generated by ASD-induced stress. In ASD, inflammatory substances such as cytokines (IL-1 and TNF) and chemokines (CXCL8) could be generated by brain microglia and mast cells (MCs). Here, we report that the anti-inflammatory cytokines IL-37 and IL-38 may be involved in ASD, which could offer new therapeutic aspects for this disorder of unknown pathogenesis that mainly afflicts children.

KEYWORDS: *autism spectrum disorder, blood-brain barrier, inflammation, immunity, cytokine*

INTRODUCTION

Autism, or autism spectrum disorder (ASD), is a neurodevelopmental disease with functional disabilities caused by brain dysfunction that usually begins before the age of 3 years old. Between the years 2012-2021, 1 in 100 children were affected by ASD and the incidence is increasing (1). In fact, today it is estimated that in the United States, approximately 1 in 60 children are affected by the disease (2). Furthermore, the diagnosis of ASDs has increased more than tenfold in the past 20 years (3).

Individuals with ASD have impaired communication and social interaction, display abnormal behaviors due to sensory hyper-reactivity or hypo-reactivity, and can show pervasive developmental disorder, epilepsy, and intellectual disability (4). The disease can have varying degrees of severity and the causes are not yet known. People with ASD have a normal phenotype that does not distinguish them from other individuals. Some affected individuals may have sufficient verbal communication skills, while others may be nonverbal and need help in their daily lives. Individuals with ASD may also have mental health problems such as anxiety, hyperactivity, depression, and attention deficit disorder, although these disorders can also occur in individuals without ASD (5-7). Subjects with ASD do not have altered diagnostic signs, such as different clinical analyses compared to normal subjects, and therefore diagnosing the disease is difficult. Since there is no biochemical or genetic screening test at the moment, the only available diagnosis seems to be based on the anomalous behavior of the subject affected by the disease.

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The cause of ASD is unknown, although genetics plays a strong role, and many hypotheses and theories have been reported suggesting the risk factors for disease development (8,9). The idea that vaccines could cause ASD has been disproved by several major studies (10,11). Moreover, since the disease is of unknown etiology, there is no specific pharmacological therapy and as ASD manifests with different degrees of severity, behavioral therapies should be applied individually.

Pathogenesis of autism spectrum disorders (ASDs)

The blood-brain barrier (BBB) is formed by endothelial cells, pericytes, and immune cells, and protects the brain from the entry of toxic molecules transported by the blood. Although there is no correlation between intestinal symptoms and ASD, children with ASD often have gastrointestinal symptoms such as pain, diarrhea, and intestinal dysfunction, which can lead to the absorption of harmful substances that could pass through the still-unformed BBB to reach the brain, somehow causing damage and leading to ASD (12). Autistic subjects are more prone to stress, with greater hypothalamic-pituitary-adrenal axis activity and higher cortisol levels than non-autistic subjects (13).

There are different genetic, environmental, allergic, and infectious factors that could increase the risk of ASD, which could involve immune cells such as mast cells (MCs) (14). MCs derive from marrow cells and reside in vascularized tissues (15). They are activated through the binding of IgE on the FcεRI receptor, which by aggregating allows the release of biologically active compounds (16). MCs mediate innate immunity, including inflammatory disorders, and acquired immunity (17). FcεRI activation leads to cell degranulation and the immediate release of preformed mediators, including tumor necrosis factor (TNF), and subsequently, after some hours, MC activation generates cytokines and chemokines by *de novo* synthesis (18). Several immune cells, including MCs, produce IL-1 which recruits neutrophils, induces TNF and IL-6, and increases inflammation (19). In addition, TNF derived by MCs activates immune cells such as macrophages that participate in the inflammatory reaction (20).

Brain MCs are activated in a state of acute stress and can release corticotropin releasing hormone (CRH) which increases vascular permeability and facilitates the passage of harmful substances to the central nervous system (CNS) (21). Experiments on rodents have shown that stress stimulates intestinal MCs, an event that can also happen in some allergic reactions (14,22). The activation of intestinal MCs in children with ASD, who have an undeveloped BBB, would lead to the release of vasoactive and inflammatory molecules, such as cytokines that could cross the BBB to reach the brain and damage it (14). Thus, in autistic children, several allergens could trigger and activate gastrointestinal MCs, producing molecules such as cytokines and pro-inflammatory toxins that would increase BBB permeability, and then subsequently reach the CNS, causing neuroinflammation. However, these hypotheses still need to be confirmed by further studies. Histamine, serotonin, prostaglandins, TNF, vascular endothelial growth factor (VEGF), and vasoactive intestinal peptide (VIP) are molecules produced by activated MCs that could increase vascular permeability. The increase of these immune molecules in the brain could contribute to ASD.

From literature data, the immune system seems to be increasingly involved in the pathogenesis of ASD (23-29). In fact, it seems that in subjects with ASD, pro-inflammatory molecules such as IL-1, TNF, and some chemokines, including CXCL8, are increased both in serum and in cerebrospinal fluid (30,31). The increase of neuropeptides such as neurotensin stimulates the gene expression and secretion of the cytokine IL-1 and the chemokine CXCL8 in microglia (32). The activation of microglia can lead to brain abnormalities that contribute to ASD (33).

IL-37, which was previously known as IL-1F7, is an IL-1 family member whose pro-IL-37 is cleaved by caspase-1 into biologically active mature IL-37. If IL-1 is important in the pathogenesis of ASD, the inhibition of IL-1 with IL-37, a naturally occurring IL-1 immunosuppressant cytokine, could represent a new therapeutic strategy for this neurological disease. Microglia activation leads to increased gene expression of IL-18 and its receptor IL-18R, mediating the inflammatory phenomenon (Fig.1).

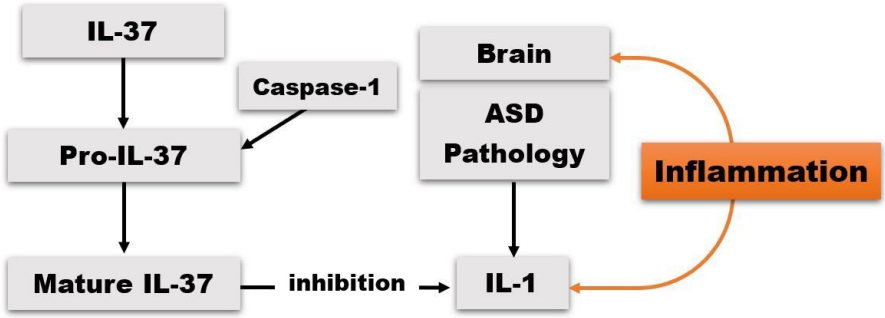

Fig. 1. *The autism spectrum disorder (ASD) brain may secrete IL-1 which induces inflammation, an effect that could be inhibited by mature IL-37.*

The increase in IL-37 expression may have a protective action against some pro-inflammatory cytokines such as IL-1. IL-37 gene expression is increased in ASD, a reaction that attempts to suppress inflammation (32) (Fig.2).

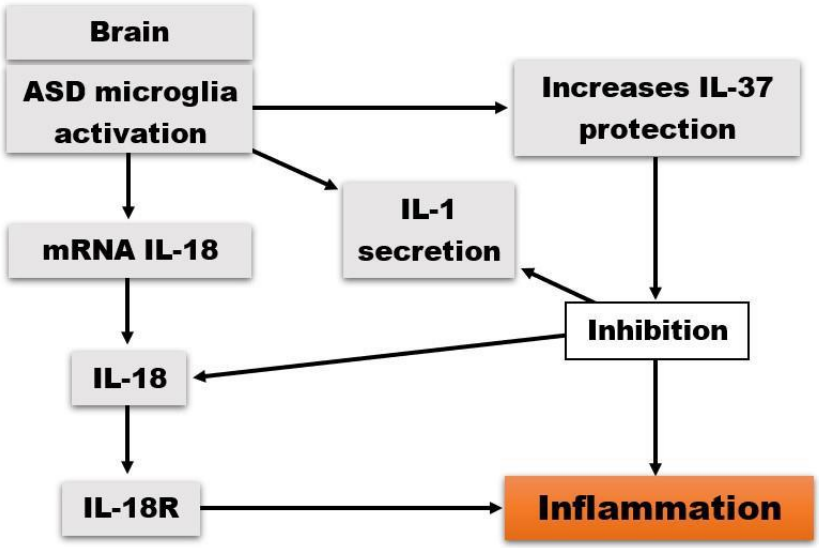

Fig. 2. *Microglia from the autism spectrum disorder (ASD) brain may release inflammatory cytokines such as IL-1 and IL-18, which can be inhibited by the anti-inflammatory cytokine IL-37, which gives protection against IL-1 family members.*

The cytokine IL-38 also derives from the IL-1 family and has an anti-inflammatory power. This cytokine is found within the macrophage and must be cleaved at the N-terminal portion before being secreted extracellularly in an active form (34). The activity of this anti-inflammatory cytokine is carried out after binding to the IL-36 receptor (IL-36R) and the coreceptor IL-1 receptor 9 (IL-1R9) (35). It has been recently reported that IL-38 can inhibit the secretion of stimulated pro-inflammatory molecules from cultured human microglia (36). IL-38 is a more potent inhibitor than IL-37, and in the brains of children with ASD, there is reduced gene expression of IL-38 and its receptor IL-36R, demonstrating that this cytokine plays a key role in the inhibition of microglial activation (36) (Fig.3).

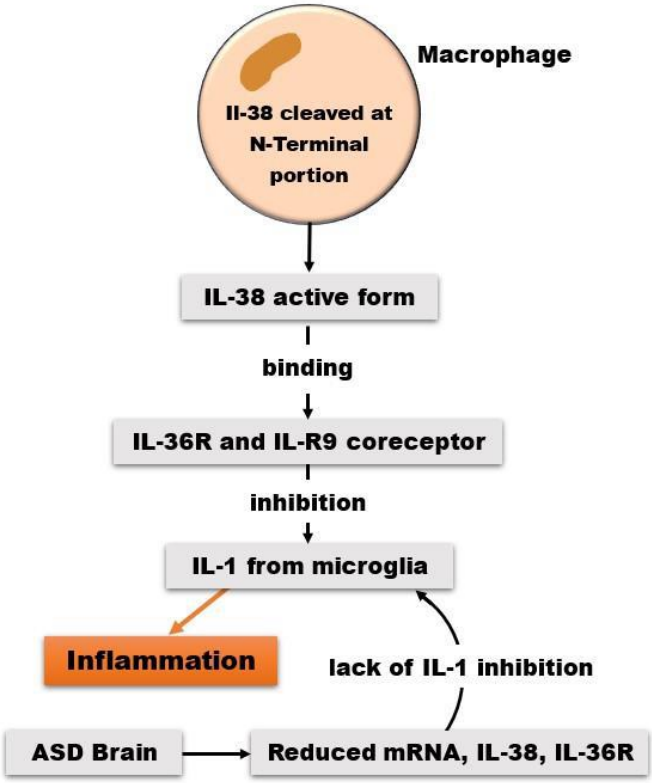

Fig. 3. *Inside the macrophage, IL-38 is cleaved at the N-terminal portion and is released extracellularly as its active form. Mature IL-38 binds the IL-36 receptor and the IL-R9 coreceptor, inhibiting IL-1 secreted by microglia. In the autism spectrum disorder (ASD) brain, mRNA, IL-38, and the IL-36R are reduced, causing the lack of inhibition of IL-1 from microglia, and therefore, inflammation.*

The pretreatment of cultured human microglia with recombinant IL-38 inhibits the neurotensin-stimulated secretion of two important pro-inflammatory molecules: IL-1β and CXCL8 (36). Additionally, gene expression of IL-38 and its receptor IL-36R was decreased in the amygdala of ASD patients (36).

However, increased IL-38 levels could signify a physiological opposition to IL-1-induced inflammation, while a decrease in IL-38 could favor the effect of IL-1. Therefore, variations in the level of IL-38, both in a positive and negative sense, could indicate an inflammatory process in progress.

CONCLUSIONS

In conclusion, ASD is a neurodevelopmental disease with brain disabilities including impaired verbal communication and social interaction, even if affected individuals do not have impaired diagnostic signs. The pathogenesis of this disease is unknown, although it is hypothesized that harmful substances developed in the gastrointestinal tract during childhood could cross the BBB, reach the brain and cause neuroinflammation. Moreover, allergies and intestinal inflammation could activate MCs, leading to the release of pro-inflammatory substances. Activated MCs and brain microglia cause inflammatory substances, such as the cytokines and chemokines IL-1, TNF, and CXCL8, to be released.

Here, based on the data reported in the literature, we hypothesize that the anti-inflammatory cytokines IL-37 and IL-38 may be involved in ASD and might have an inhibitor effect on inflammatory cytokines, which could be useful for therapy treating this disorder.

Conflict of interest

The authors declare that they have no conflict of interest.

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NEUROPATHOLOGY AND NEUROINFLAMMATION IN AMYOTROPHIC LATERAL SCLEROSIS

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) disease is mainly caused by the death of motor neurons, and usually strikes in old age with a rapid course, typically resulting in fatality about 4 years after diagnosis. The death of motor neurons interrupts synapses with muscles which leads to muscle atrophy with stiffness, spasticity, and subsequent death of the patient. There are various causes of neuronal dysfunction and death, including mitochondrial malfunction, impaired axonal transport, caspase activation, and inflammatory cytokine production. In line with other neurological diseases, the immune system may be involved in ALS. Immune cells such as microglia, Treg cells, and T helper cells (TH) intervene early in the disease to defend and protect the central nervous system (CNS). Subsequently, microglia/M1, TH1, TH17, and other cells, are activated to produce inflammatory cytokines that aggravate the pathological state of ALS. In this paper, we discuss the neuropathology and neuroinflammation that occurs in ALS, a fatal disease that still needs in-depth studies.

KEYWORDS: *amyotrophic lateral sclerosis, neuroinflammation, neuropathology, neurodegeneration, immunity, CNS*

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that affects motor neurons in the brain and medulla. The disease is late onset and involves a rapid course of progression, resulting in paralysis and eventual death (1). Affected individuals have muscle weakness which involves the diaphragm, an effect that leads to death generally after about 4 years (2). The lower motor neurons responsible for the innervation of muscles reside in the motor cortex of the brain, in the brainstem, and in the spinal cord. Motor neuron failure leads to muscle dysfunction that is characterized by stiffness and spasticity. The affected lower neurons degenerate and are no longer able to synapse with muscles, causing muscle atrophy. Muscles of the eye and the sphincter are the least affected by the disease (3). Within 30 months of the onset of symptoms, about half of the patients affected by this pathology die (4), often due to respiratory insufficiency (5).

ALS diagnosis is made through electromyography and laboratory analyses. The disease does not appear to be genetic, although some individuals do have a family history of ALS (6). Some protein-coding genes have been associated with the disease, where there is mitochondrial dysfunction, protein aggregation with dysfunction of homeostasis or protein clearance defect, impaired RNA metabolism, impaired axonal functioning, and DNA damage due to defective DNA repair

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mechanisms (6-8). Current therapies are not very effective, as they have undesirable side effects and improve survival by only a few months (9). The physiopathology of ALS is unknown, and therefore, to identify new therapeutic targets, more knowledge of this disease is needed, both at the genetic and neuroinflammatory levels.

DISCUSSION

Although significant progress has been made by studies researching the risk factors and the genetic basis of ALS in recent years, further investigation and clarification are still needed. Today, we know that the risk factors include increasing age and the male sex, and it appears that specific environmental exposure also plays a role in disease development (10). Motor neuron injury and dysfunction occur in ALS due to various possible causes, some of which are reported in the table below (Table I).

Table I. *Possible causes of motor neuron injury occurring in ALS.*

- mRNA and mitochondrial dysfunction
- Calcium toxicity
- Glutamate excitotoxicity
- Modified protein toxicity
- Impaired autophagy
- Impaired axonal transport
- Reactive oxygen species (ROS) formation
- Caspase activation with IL-1 production
- Endoplasmic reticulum (ER) stress

These malfunctions contribute to neuroinflammation in ALS and exacerbate the pathology. Some authors have found a correlation between blood lipid levels [low-density lipoprotein (LDL) cholesterol and total cholesterol] and ALS risk (11,12). In addition, it appears that exercise, type 2 diabetes, atherosclerosis, and cardiovascular disease (13-16) are linked to ALS, and it has been suggested that a favorable vascular risk profile may increase susceptibility to the disease (17).

Dysfunctional immunity may also be involved in the onset of ALS, as we know that this feature is common to neurological diseases (18). In ALS, the cooperation between motor neurons and glial cells, which is necessary to maintain the active physiological state of the brain, appears to be compromised. Microglia are macrophagic immune cells that intervene early in the disease as a neuroprotective factor which subsequently transforms into a neurotoxic factor, an effect that is counteracted by Treg and TH immune cells (19). Immune cells initially intervene in the disease by producing anti-inflammatory cytokines, such as IL-10, to protect motor neurons, but as the disease worsens, it leads to the activation of microglial/M1 cells and T cells, contributing to the pathology that occurs in ALS (20,21) (Fig.1). Dendritic cells also participate in the disease and have been found to be reduced in circulating blood (22) yet increased in the spinal cord (23) in ALS patients when compared to unaffected individuals. These cells can present harmful antigens to T lymphocytes and can contribute to the inflammatory state by producing cytokines that mediate motor neuroinflammation.

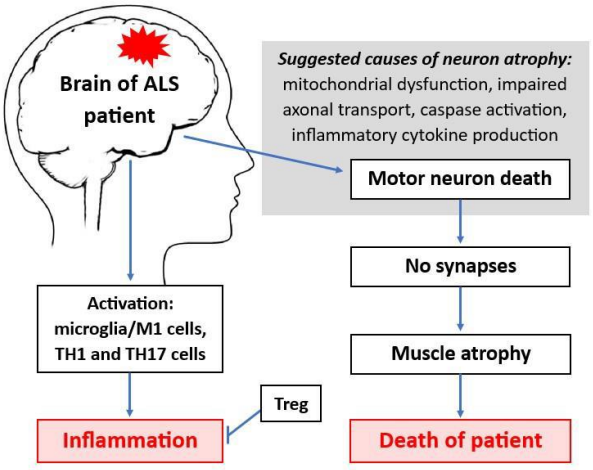

Fig. 1. *The brain of patients affected by ALS is characterized by the death of neurons which disrupts synapses and neural connections, causing muscle atrophy and the subsequential death of the patient. In addition, in ALS patients, there is*

activation of microglia/M1, TH1, and TH17 cells, which mediate inflammation, an effect that can be inhibited by Treg cells.

T cells play an important role in acquired immunity and can be found in infiltrating brain tissue. They are very important in the progression of ALS. In fact, the CD4+ T helper subpopulations, together with CD8+ lymphocytes and microglia, participate in the late phase of the neuroinflammatory reaction (24). The CD4+ cells which are the most involved in ALS are Tregs, TH1, TH2, and TH17, with Tregs and TH2 cells having neuroprotective effects, and TH1 and TH17 cells mediating neuroinflammation (25,26). Since protective Treg cells are no longer effective and decrease in number in ALS, the neurotoxic phenomenon prevails with devastating motor consequences.

ALS studies have utilized transgenic mice in which the genetic composition has been modified by the insertion of exogenous DNA (27). Using SOD1G93A animals showing the loss of small cutaneous fibers, similar to that which occurs in patients with ALS, it has been noted that immune and glial cells influence the pathophysiological state of motor neurons. Transgenic mice that selectively express SOD1 in their motor neurons do not have the disease or it occurs later (28). However, microglia and astrocytes in wild mice provide a protective function by opposing the disease.

Some authors have reported that the variation in the number of leukocytes in the blood can be correlated with the onset of ALS (29). Another hypothesis correlates onset with the inflammatory response mediated by some cytokines and their receptors (30). Immunological studies of the disease have shown a correlation with an increase in white blood cells in affected patients, although the levels of inflammatory cytokines do not appear to change compared to unaffected subjects (31,32).

In an interesting article, Ching-Hua Lu, et al. (31) reported that ALS patients showed a downregulation of interferon-gamma (IFN-γ) and a nonuniform upregulation of some inflammatory cytokines in peripheral blood. These upregulated cytokines included tumor necrosis factor (TNF), IL-1β, IL-2, and IL-8, amongst others. Regarding IL-6, the authors showed that this cytokine is elevated in the advanced stage of the disease and could represent a therapeutic target (31). Elevated levels of the neuroinflammatory molecule TNF may also be associated with the disease since this cytokine is involved in motor neuron damage. However, peripheral plasma analysis demonstrated that the cytokines IL-6, TNF, and IFN-γ were the most highly regulated markers (31). The authors concluded that ALS is related to the systemic regulation of inflammatory cytokines acting on T lymphocytes that regulate the immune response (31). Treg cells play an important protective role in the neurodegeneration that occurs in ALS and many different pathologies of the central nervous system, while TH-17 mediates the neuroinflammatory process.

CONCLUSIONS

To date, studies conducted on ALS have shown that the disease pathogenesis involving motor neuron death is complex, and that gene mutation and neuroinflammation certainly play a key role. The disease initially follows a slow course neuronal injury that is mediated by different mechanisms and counteracted by immune cells including M2 microglial cells and Treg cells. Later, when M1 microglial cells and TH1 and TH17 cells are activated, ALS worsens, and degeneration follows a faster course. The cause of this disease remains unknown, although the misfolded SOD1 protein, and other abnormal proteins and peptides, can activate immune cells which leads to the production of inflammatory molecules such as cytokines and other compounds which aggravate ALS.

Conflict of interest

The author declares that they have no conflict of interest.

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THE IMPACT OF MAST CELLS IN NEUROIMMUNOLOGY AND CANCER

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ABSTRACT

The nervous system and immune system are connected by bidirectional pathways, and behavioral influences can have effects on immune functions. Immune system stress can have regulatory effects in neuroinflammation, allergic reactions, cancer growth, and other conditions. Additionally, pyschological stress can aggravate different conditions such as atopic dermatitis, rhinitis, and asthma. Mast cells (MCs) are immune cells derived from the myeloid lineage which migrate to peripheral tissues to differentiate and mature. They play an important role in the innate and adaptive immune responses, where the physiological and pathological aspects are regulated by the activation and degranulation of MCs. This includes immune responses such as those involved in infection, allergic disease, stress, and tumor growth. MCs cells are ubiquitous in the body, and have a close anatomical and functional relationship with neurons and neuronal processes in the central and peripheral nervous systems. MCs are rich sources of biologically active preformed mediators, which are contained in secretory granules. These cells can differentially and selectively release their mediators, and utilizing this selective release process in treatment could offer therapeutic opportunities for cancer, hypersensitivity reactions, and neuroinflammation.

KEYWORDS: *mast cell, neuroimmunology, neuroinflammation, immune, cancer*

INTRODUCTION

There is evidence indicating that the nervous system, which communicates with the whole organism, can regulate cancer growth directly or through the immune system. Published studies have indicated that stress may have a permissive effect on cancer growth (1-4), neuroinflammation, and other conditions, and it has now been established that stress can produce definitive changes in the make-up and function of the immune system (5,6). Moreover, there is much discussion concerning psychoneuroimmunoendocrinology that studies the interplay between the psyche, neural, and endocrine functions and immune responses, and the applications of these effects on the immune response and cell proliferation (7-10).

Allergic reactions have been shown to have neuropsychologic elements that comprise a close association between the immune system and the nervous system (11). These cases involve a disease pathophysiology that cannot be accounted for solely by elevated levels of immunoglobulin E (IgE) and antigen (Ag). Different studies have shown the

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psychoneuroimmunoendocrinologic association in allergic reactions such as atopic dermatitis (AD), rhinitis, and asthma, which can be induced or aggravated by compounds of the nervous and endocrine systems and are linked to psychological stress (12-16).

Mast cells (MCs) are immune and inflammatory cells that play an important role in the innate and adaptive immune systems. Additionally, they are the main effector cells implicated in allergic or anaphylactic reactions. Paul Ehrlich first identified these cells in 1878 using a staining process to show the multitude of granules they contained (17). MCs are derived from immature pluripotent hematopoietic progenitors in the bone marrow, and then migrate through the vasculature system to reach peripheral tissues where they differentiate and mature in a tissue-specific manner (18-21). The activation and degranulation of MCs regulates many physiological and pathological aspects, including the initiation and the continuation of inflammatory responses, including those in the central nervous system (CNS).

These cells are ubiquitous in the body and their membrane-bound secretory granules contain biologically active preformed mediators (22). During allergic immune reactions, MCs are triggered by IgE and Ag, as well as diverse neuropeptides. MCs are localized in association with the CNS and the peripheral nervous system, where they are directly innervated and have a close anatomical and functional relationship with neurons and neuronal processes (23). For this, it is suggested that MCs also have a close association with neurotransmitters and neuropeptides where there is likely bidirectional regulation.

MCs are located around the vasculature and are present in brain tissue, particularly in the hippocampus, thalamus, and hypothalamus (24). MC mediators may influence the physiopathology of the body, including the response to stress by regulating the levels of peptide hormones available in the hypothalamic-pituitary axis and the production of proinflammatory and antinflammatory molecules.

MCs are involved in the induction and development of immune responses in response to infection, allergic disease, and, although the mechanisms are still unclear, stress and tumor growth. The tumor microenvironment is made up of fibroblasts, adipose cells, immune-inflammatory cells, the extracellular matrix, and blood and vascular networks (25). It has been shown independently both *in vitro* and *in vivo* that MCs undergo differential or selective release of their mediators, a process that occurs without degranulation that might operate using vesicular shuttles utilizing specific mediator binding proteins (26-28). Inducing the selective release of MC mediators or selectively inhibiting MC degranulation after appropriate stimulation could result in either enhancement or suppression of tumor growth. Such a process could enhance science's understanding of the pathophysiology of cancer, type I and VI hypersensitivity reactions, and neuroinflammation, and could provide new therapeutic opportunities.

Mast cells and neuroinflammation

Neuroinflammation is a hallmark of neurodegenerative diseases, with MCs playing an important role in this process. The immune system initiates the protective response of inflammation to repair and heal damage inflicted by injury, bacteria, or other harmful insults. Neuroinflammation is the inflammatory response that occurs in the CNS which can be detrimental if it is prolonged. Chronic neuroinflammation can inhibit regeneration and lead to brain injury (29), and it is a characteristic feature of diseases such as Alzheimer's disease (AD) (30,31), Parkinson's disease (PD) (32), and amyotrophic lateral sclerosis (ALS) (33). Interactions between glial cells, immune cells, and neurons can produce and sustain neuroinflammation. Microglia and astrocytes mediate innate immune responses in the brain that can be activated by proinflammatory stimuli that are released from immune cells such as MCs. MCs produce various inflammatory mediators including histamine, proteases, growth factors, chemokines, and cytokines. MCs are normally found in low numbers in the brain (34), but increased numbers of these cells have been observed during trauma, stress, infection, and in some CNS diseases such as stroke (35) and multiple sclerosis (36,37). MCs participate in neuroinflammation by interacting with glial cells and neurons, and effecting blood-brain barrier (BBB) permeability and neurodegenerative processes such as neuronal death, excitotoxicity, and synaptic dysfunction (38).

Microglia and MCs can interact by complex unidirectional or bidirectional cross-communication. For example, tryptase released from MCs activates microglia (through PAR2 receptors) to release reactive oxygen species (ROS), tumor necrosis factor (TNF), and IL-6 (36,39). However, due to their prestored granule supply of mediatory substances such as immunomodulators, neuromodulators, proteases, growth factors, and amines, MCs can act quickly to injury and insult and are increasingly being considered as first-responders in the immune response in the CNS (40). MC degranulation releases gonadotropin hormone-releasing hormone (GnRH), monoamines, proteases including chymases, tryptases, carboxypeptidase, cytokines, and histamine (41,42), which exert effects on nearby cells (e.g. T cells) that enter the brain through the compromised BBB in states of infection and inflammation. Additionally, these MC-released compounds activate microglia, which go on to release pro-inflammatory cytokines that exacerbate the inflammatory state. Due to their close proximity, microglia and MCs interact and affect each other through paracrine mechanisms (38).

Finally, MCs may be involved in stress-related neuroinflammation and neurodegeneration. Chronic stress has been linked to neuroinflammation, which it seems to exacerbate, and increases the risk of neurodegenerative diseases such as AD (43, 44). During stress and inflammation, molecules such as corticotropin-releasing hormone (CRH) are released by MCs, which activate microglia cells and pro-inflammatory processes, suggesting that MCs are involved in stress-related neuroinflammation and neurodegeneration (45).

Mast cells in hypersensitivity reactions

MCs derive from the bone marrow and then migrate into peripheral tissues to mature. The maturation of MCs is dependent on microenvironmental conditions such as the presence of IL-3, IL-6, stem cell factor (SCF), and other growth factors released from activated T-cells (46,47). Activated mucosal MCs and those from bone marrow can secrete inflammatory proteins without degranulation. MCs which mature in the presence of IL-3 also express IL-2 receptors (48), and IL-2 additionally promotes the generation of lymphocyte-activated killer (LAK) cells, as well as CD8+ T cells and natural killer (NK) cell cytolytic activity (49).

Cytotoxic T cells that express CD8+ are the strongest effectors in the immune response against cancer (50), and the interaction between MCs and Tregs can influence the intensity of tumor-induced inflammation, resulting in the inhibition or promotion of the growth of tumors (51). Therefore, the MC-Treg relationship may offer useful therapeutic options for tumor immunotherapy.

Lymphocyte products, such as IL-1, can trigger or increase MC secretion (52,53), and the early release of MCs could be related to the delayed response of T-cells (54), a process that may be linked to allergic reactions which include a late phase component (55).

Studying the relationship between MCs and T-cells, and their possible regulation by neuroendocrine or tumor-generated substances, could provide the basis for new therapies.

The role of mast cells in tumor growth

As early as 1877, MCs were seen at tumor sites (56) and as time progressed, were subsequently suspected to be involved in the growth of tumors (57). It is now clear that these immune cells proliferate around tumors and in the tumor microenvironment during disease progression. The accumulation of MCs has been seen in a variety of tumors including epidermoid carcinoma (58), adenomatous polyps (59), rat mammary adenocarcinoma (60), pancreatic β-cell tumour (61), cervical carcinoma (62), and melanoma (63).

Tumor-secreted factors recruit and activate MCs, with the primary one being SCF (64). However, fibroblast growth factor (FGF)-2, vascular endothelial growth factor (VEGF), platelet-derived endothelial cell growth factor (PD-ECGF), RANTES, monocyte chemotactic protein (MCP)-1, adenosine, and adrenomedullin have also been seen to recruit and/or activate MCs to the tumor site (65-67).

MC accumulation is also correlated with vascularization, with increased numbers of MCs seen in highly vascularized areas of certain tumors (62,68,69). An association has also been reported between MC migration and new vessel formation in breast, colorectal, and uterine tumors (68,70,71). The perivascular location of MCs, and the fact that they can release vasoactive agents, links these immune cells to the support and maintenance of the vasculature and angiogenesis (72,73). Interestingly, MCs accumulate at tumor sites before new capillaries are formed (73). In fact, MCs contain and secrete mucopolysaccharide heparin, which causes capillary endothelial cell migration *in vitro* (74).

Numerous normal tissues produce a small amount of VEGF, but this process is tightly regulated, and the endothelial growth factors are minimally expressed in normal conditions (75), contrasting the high rate of expression that occurs in tumors where angiogenic factors appear to be continuously expressed (76). Tumor-derived peptides attract MCs to the tumor site where they can secrete heparin within the collagenous stroma (77). A track, or path, is formed behind the migrating MCs as they partially release this heparin, which could direct the movement of sprouting capillaries towards the direction of the tumor (74). Growth factors such as nerve growth factor (NGF) (78), as well as IL-1 produced by macrophages, which are abundant in proliferating tissues, induce MC degranulation.

Histamine from MCs can stimulate local cell proliferation, which has been seen by the rapid growth of cells neighboring to activated degranulated MCs (79). MC-derived histamine also activates T-suppressor cells, which can inhibit the immune system (80,81).

The antitumorigenic functions of mast cells

While MCs have effects that favor tumor growth and are associated with unfavorable prognosis, they also show inhibitive effects as well. In fact, MC infiltration at tumor sites has sometimes been associated with favorable prognosis. Studies have shown that the presence of MCs in some colon cancers such as colorectal cancer has positive effects and

increases survival (82-84). Additionally, MC infiltration has also been correlated with improved prognosis in prostate carcinoma (85) and breast carcinoma (86). Whether MCs have pro- or anti-tumorigenic effects against cancer could depend on the nature of local MC subsets and the particular stimuli within the tumor microenvironment (87).

MCs can have cytotoxic activity and recruit and activate immune cells at the tumor microenvironment. They can directly interact with tumor cells, release different mediators that modulate the immune response at the tumor microenvironment, and by producing cytokines and chemokines, recruit other immune cells to the tumor site (87). MCs have been seen to have a selective action against tumor cells, showing cytotoxic activity to tumor cells in a preferential manner that does not harm other cells, such as fibroblasts (88).

Serine proteases from basophils have cytotoxic actions against tumor cells, and MCs are a rich source of these proteases which are stored in large amounts in the cytoplasmic granules of MCs and are also released in the process of degranulation (89).

Further evidence with MC-deficient W/Wv mice has shown that tumor growth incidence is lower after subcutaneous treatment with 3-methylcholanthrene, when compared with normal congenital mice following the same treatment (88,90). When the carcinogen was given after the MC deficiency had been overcome by bone marrow transplantation, this increased tumor incidence was seen at normal levels (88,90).

Vasoactive amines that are released by MCs could also contribute to the modulation of the tumor microenvironment.

Studies have shown that late hypersensitivity reactions involving killer T-cells are dependent on the early MC secretion of certain vasoactive mediators (54), a process which could be vital for the immune system to launch an effective defense against cancer cells. T-cells that are recruited by MCs may then proceed to secrete cytokines, which further stimulate the secretion of MCs (91). Considering this, tumor cells may play a selective role in inhibiting or promoting the secretion of specific MC mediators. It has been reported that MCs located very close to growing tumor cells had been inhibited and were unresponsive to the regular secretagogues (92), and that certain polyamines found in growing tumor cells impede MC degranulation (93-95).

CONCLUSIONS

MCs are well known for their involvement in allergic reactions, but they are increasingly being implicated in other physiological and pathological conditions. In the brain, MCs partake in complex interactions with microglia and participate in neuroinflammation, effecting the permeability of the BBB and neurodegenerative processes such as neuronal death, excitotoxicity, and synaptic dysfunction. It is known that the nervous system, with the production of neuropeptides, can influence both tumor onset and growth. MCs, the immune elements that mediate both inflammation and the body's defense, play an important role in this stage. Neuropeptide-activated MCs can release proinflammatory molecules such as cytokines that aggravate the tumor state, while they can also produce molecules that oppose tumor growth. Further definition of the role of MCs is needed to uncover their actions in neuroimmunology and tumor growth, and to identify MC-targeted treatments.

Conflict of interest

The author declares that they have no conflict of interest.

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