European Journal of Neurodegenerative Diseases
ISSN 2279-5855 / 2017 vol. 6, ISSUE N. 2, July-December

NF-κB ACTIVITY IN ALZHEIMER'S DISEASE

I. Robuffo[1*] and A. Palmieri[2]

[1]Institute of Molecular Genetics, National Research Council, Section of Chieti, Chieti, Italy;
[2]Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy.

Correspondence to:
Iole Robuffo, MD
Institute of Molecular Genetics,
National Research Council,
Section of Chieti,
Chieti, Italy.
e-mail: iole.robuffo@cnr.it

ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disease and is the most common type of dementia. In the USA, the disease affects approximately 5 million individuals, and it is expected that this number will increase drastically with the increasing age of the elderly population. Affected patients first experience mild memory loss which worsens as the disease progresses, and results in cognitive decline and ultimately, death. AD affects the brain with deposits of abnormal proteins and neuronal death. As of date, therapeutic options are limited and effective treatments still need to be discovered. Nuclear factor-κB (NF-κB) is a transcription molecule containing binding sites for genes involved in neuroinflammation and regulates genes that control cell replication and death. Gene therapy utilizing the signaling pathway of NF-kB in the brain could be targeted for gene therapy to treat AD. Blocking NF-kB could yield anti-inflammatory effects for the disease, leading to the suppression of growth hormone (GH), insulin-like growth factor (IGF-1), cell death, and also inflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor (TNF) that are involved in the pathogenesis of AD.

KEYWORDS: *Alzheimer's disease, neurodegenerative disease, dementia, gene therapy, NF-κB, inflammation*

INTRODUCTION

Alzheimer's disease (AD) is a progressive brain disorder and is the most common type of dementia (1). At present, in the USA, approximately 5 million individuals are diagnosed with AD, and this figure could reach 13.8 million over the next 40 years, with the increasing age of the elderly population (2). Such an increase will come with a heavy clinical burden for society.

In this disease which can appear after the age of 65, there may be symptoms such as disorientation, mood swings, memory loss, problems with speech, depression, and hypertension (3). Furthermore, patients may present complications such as dehydration and infectious bacterial diseases (4). AD occurs particularly in elderly subjects with evidence of cerebral Lewy bodies and vascular alterations. Diagnosis can be made by utilizing cerebrospinal fluid (CSF) biomarkers and positron emission tomography (PET) (5). In recent years, the understanding of AD has seen considerable progress but there is still much to discover in this debilitating disease.

Received: 02 September, 2017
Accepted: 07 October, 2017

2279-5855 (2017)

DISCUSSION

AD presents with amyloid plaques and neurofibrillary tangles (NFTs) in the CNS, with a decline in cognitive functioning and neuronal loss (6). The disease is caused by the improper cleavage of the amyloid precursor protein which forms abnormal β-amyloid (Aβ) which, by joining fibrils, forms Aβ plaques (7). The accumulation of abnormal proteins and the formation of plaques can last for several years before there are any symptoms of the disease.

In this disorder, amyloid angiopathies, neuritis, glial polyps, and glial response may be noted. These pathological signs cause neuronal and synaptic dysfunction with neurodegeneration and tissue atrophy. Aβ plaques are mainly formed by abnormally folded Aβ that are made up of 40 to 42 amino acids (8). The deposition of Aβ occurs in the iso-cortex, which influences the subcortex (9). The most abundant Aβ in the plaques is Aβ42, which is present in higher quantities than Aβ40 as it is less soluble (10). In the CNS, NFTs are formed by conjoined helical filaments made of hyperphosphorylated tau protein which is a microtubule-associated protein that stabilizes microtubules (11). This protein initiates and spreads in the medial temporal lobe cortex and hippocampus without invading motor, sensory, and visual areas. The severity of AD depends on the severity of neuronal and synaptic damage, and also the amount of Aβ formed (12). The genetic mutations that occur in AD are related to the formation of Aβ, leading to the generation of abnormal and pathological Aβ and resulting in neuronal dysfunction and neurodegeneration mediated by inflammation (13).

In this disease, neuroinflammation is involved and is decisive in the progression of neuropathological mutations (14,15). Activated immune cells are found within close proximity to, as well as inside, the plaques (16), and anti-inflammatory treatments have been seen to delay the onset of AD (17). Therefore, nonsteroidal anti-inflammatory drugs (NSAIDs) may help prolong the period before onset. NSAIDs block COX-2, resulting in inhibition of inflammatory prostaglandins that are induced by IL-1 and are involved in fever (18).

Nuclear factor kappa B (NF-kB) is a protein complex that functions as a transcription factor for protein production, including cytokines and chemokines. It is hypothesized that NF-kB is a key molecule that controls inflammation and apoptosis in many pathologies, including AD (19). Inflammation is known to play a key role in the pathophysiology of psychiatric diseases by involving pro-inflammatory cytokines such as IL-1 and tumor necrosis factor (TNF) (20,21). In AD, the plaques show signs of activated immunity and inflammation driven by IL-1 which, by binding to its receptor IL-1R on the cell membrane, leads to the formation of MyD88 with consequent activation of NF-kB and protein transcription (Fig.1) (22). TNF is also a highly inflammatory protein, which by binding to its receptor TNFR, activates IKKα, β, γ, with consequent activation of NF-kB and transcription of the protein (23) (Fig.2).

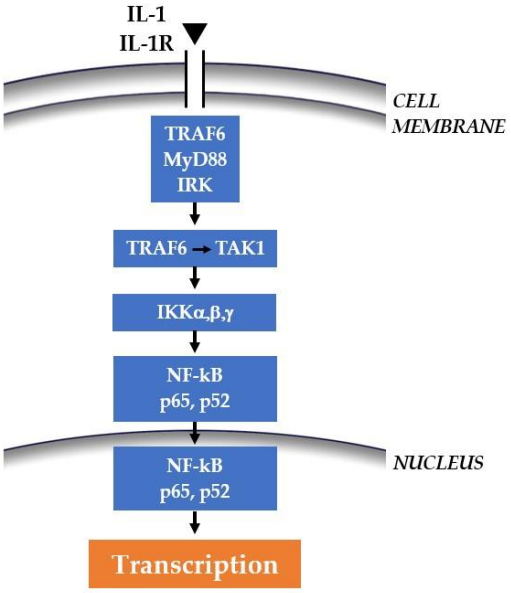

Fig. 1. *By binding its receptor IL1-R, IL-1 activates the cascade that leads to NF-kB and the transcription of the protein.*

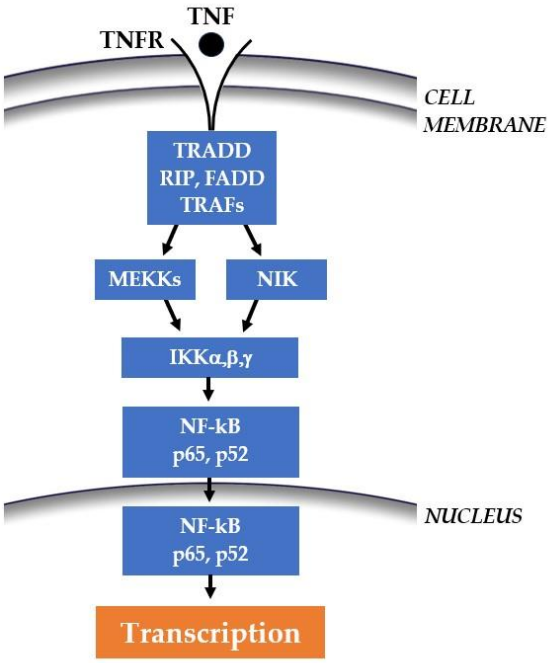

Fig. 2. *By binding its receptor TNFR, TNF activates the cascade that leads to NF-kB and the transcription of the protein.*

Although there has been progress in the study of AD in recent years, classic therapeutic strategies have not been found to be effective. Therefore, much molecular research dedicated to the treatment of AD is concentrated on gene therapy, the insertion of foreign genes into cells to genetically modify diseased cells. NF-κB is a transcription molecule containing binding sites for genes involved in brain inflammation and regulates genes that control cell replication and death (24). Therefore, some inflammatory molecules that act through the signaling pathway of NF-kB at the brain level could be targeted. A possible anti-inflammatory therapeutic strategy in AD could involve the blocking of NF-kB, since its inhibition leads to the suppression of growth hormone (GH), insulin-like growth factor (IGF-1), and cell death (25). Furthermore, blocking NF-kB also suppresses inflammatory cytokines such as IL-1 (26), IL-6 (27), and TNF (28), which play an important role in the pathogenesis of AD (29).

CONCLUSIONS

Inflammation plays a key role in the progression of AD. Pro-inflammatory cytokines such as IL-1 and TNF that are found in plaques mediate neuroinflammation through the activation of NF-kB, aggravating the pathological state of the disease. The inhibition of these pro-inflammatory cytokines and other molecules, such as prostaglandins, would certainly help improve symptoms in AD.

Conflict of interest

The authors declare that they have no conflict of interest.

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European Journal of Neurodegenerative Diseases
ISSN 2279-5855 / 2017 vol. 6, ISSUE N. 2, July-December

Letter to the Editor

ASTROCYTES PLAY A CRUCIAL ROLE IN TRAUMATIC BRAIN INJURY

R. Saggini[1*], M. Rosati[2]

[1] Physical and Rehabilitation Medicine, Department of Medical Oral and Biotechnological Sciences, "Gabriele D'Annunzio" University, Chieti-Pescara, Italy;
[2] Pescara Civil Hospital, Pescara, Italy

**Correspondence to*:
Professor Raoul Saggini,
Department of Neuroscience and Imaging,
University G. D'Annunzio of Chieti-Pescara,
Chieti, Italy.
e-mail: raoul.saggini@unich.it

KEYWORDS: *astrocyte, CNS, brain trauma, pathophysiology, neurodegeneration, inflammation*

INTRODUCTION

A traumatic brain injury (TBI) consists of physical damage to the brain tissue and is a major global cause of morbidity and disability, carrying a high socioeconomic burden (1). The damage from a TBI can be either temporary or permanent and compromises the normal functioning of the brain. There can be different types of brain injuries and the course and therapy depend on the location and severity of the damage. The pathological process that occurs after TBI is complex and many factors are involved. In recent years, this topic has been strongly debated in the scientific literature, and the in-depth study of new technologies and various therapies have led to a notable improvement in managing patients with TBI.

Astrocytes, which take their name for their star-like appearance, are important cells of the central nervous system (CNS) and spinal cord. Astrocytes constitute neuroglia and are found in both white matter and gray matter where they present some differences. They participate in many brain functions such as immune reactions, brain diseases, and trauma, with different and sometimes opposing responses. Astrocytes and macrophages are activated early by brain damage, resulting in the release of neurotoxic factors and the subsequent formation of scar tissue (2). After brain trauma, endogenous neurogenesis can occur, which contributes to spontaneous hospitalization after the damage. In this article, we discuss the functions of astrocytes within the CNS and their pathophysiological functions in TBI, which are important topics for developing new therapies.

DISCUSSION

TBIs can be separated into two types of injuries: "primary" injuries, which refers to the mechanical damage that is inflicted, and "secondary" injuries, which refers to the molecular and biological processes that occur after the initial damage. In the "primary" lesion, there is large-scale brain damage that triggers the "secondary" lesion, which consists of extensive inflammation in the CNS. This inflammatory reaction is a defensive response to the physical trauma but can also significantly aggravate the traumatic brain damage. In the "primary" lesion, immune cells including microglia, are activated. The activation of immune cells can improve the traumatic state since they synthesize helpful molecules such as growth factors. However, activated immune cells can also produce inflammatory cytokines and can therefore be very

Received: 20 November, 2017
Accepted: 15 December, 2017

2279-5855 (2017)

harmful to the ongoing pathological process. For this, developing new immunological strategies could be of great help in tackling this serious problem which too often leads to patient death (3).

Sterile inflammation is a process that always occurs in trauma, and results during the "secondary" injury in TBI (4). This is inflammation that occurs without a response to pathogens, and in which multiple types of cells participate. When an injury takes place, immune cells are recalled and activated by the immune system. These cells then go on to send signals to neurons and glia, causing them to produce inflammatory molecules such as chemokines and cytokines.

Microglial cells are elements of the non-specific innate immune response that promptly respond to antigens that are foreign to the organism, although they sometimes also react against self-antigens (autoimmunity). Microglia express toll-like receptors (TLRs) to recognize pathogens and dangerous molecules, and activation of these receptors leads to the synthesis of inflammatory proteins such as chemokines and cytokines (5).

The first lesion causes a rapid primary response, warning that the brain has suffered trauma with the release of molecules such as ATP and high mobility group box 1 (HGMB1) protein, effectors of the inflammatory state (6,7). These signals lead to the activation of TLRs, which activate myeloid cells including microglia. Furthermore, the assembly of the inflammasome (NALP1) leads to the synthesis of IL-1 and IL-18, two highly inflammatory cytokines, as well as chemokines (8) (Fig. 1). This entire reaction leads to the participation of other molecules, such as reactive oxygen species (ROS) and nitric oxide (NO), which further amplify the inflammatory response.

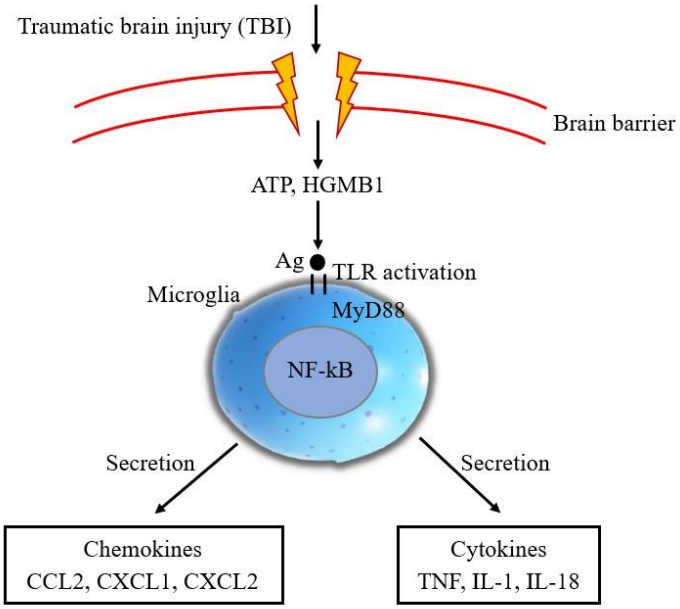

Fig. 1. *Traumatic brain injury (TBI) activates ATP, HGMB1, and antigen binding toll-like receptor on microglia cells. This reaction leads to the activation of a cascade involving MyD88 in the cytoplasm and NF-kB in the nucleus, with secretion of CCL2, CXCL1, and CXCL2 chemokines and TNF, IL-1, and IL-18 cytokines.*

The innate immune response is followed by a more specific adaptive response, with the activation of T and B lymphocytes that recognize the antigen presented by the antigen presenting cells (APC). The CD4 and CD8 T cell subclasses may have TBI-aggravating cytotoxic functions or may be helpful and regulatory. However, these cells also produce pro-inflammatory cytokines, such as TNF and IL-1, which exacerbate neuroinflammation (9). B cells participate in the activation of T lymphocytes by producing immunoglobulins. Among the latest cytokines discovered are IL-37 and IL-38 that are reported to be anti-inflammatory (10). Since pro-inflammatory cytokines exacerbate the pathological state of TBI, there is a potential role for these cytokines to be used in TBI therapy.

CONCLUSIONS

Following TBI, the activation of immune cells is helpful to repair damage, but on the other hand, the release of inflammatory cytokines and chemokines can be detrimental with neuroinflammation and aggravation to the damaged tissue. Modulation of the immune system that induces sterile inflammation could change the clinical-pathological course following TBI and therefore, more research should continue to resolve the ongoing questions.

Conflict of interest

The authors declare that they have no conflict of interest.

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European Journal of Neurodegenerative Diseases
ISSN 2279-5855 / 2017 vol. 6, ISSUE N. 2, July-December

BRAIN TUMOR AND INFLAMMATION

M.L. Castellani

Immunology Division, University of Chieti, 66100 Chieti, Italy.

Correspondence to:
M.L. Castellani PhD,
Immunology Division,
University of Chieti,
66100 Chieti, Italy.
e-mail: mlcastellani@unich.it

ABSTRACT

Innate immunity generates cytokines, including IL-1, which are important in controlling tumor development. Excessive synthesis and secretion of pro-inflammatory cytokines causes inflammation that promotes tumor development and progression. Immune cells are present in tumor tissue, including lymphocytes and monocytes that generate cytokines. These immune cells are recruited to the tumor site to fight the new tumor tissue which is not recognized as self. However, this process leads to a production of chemokines which attract immune cells, producing an excess of inflammatory cytokines that favor tumor development. Mast cells (MCs) are ubiquitous immune cells that also reside in brain tissue and participate in the brain tumor process by generating neuroinflammation. MCs are recruited by chemokines into brain tumor tissue where they become activated and produce several cytokines including IL-8, growth factors, vascular endothelial growth factor (VEGF), and also chemical mediators such as histamine and heparin, and tryptase and chymase that favor the formation of new blood vessels and mediate the production of metastases. However, MC accumulation in cancer tissue can be either beneficial or detrimental for tumor development.

KEYWORDS: *brain, tumor, inflammation, cytokines, chemokines, immune response*

INTRODUCTION

Chronic brain inflammation is mediated by cytokines and chemokines, which are generated by innate immunity and can have effects on the growth of tumors (1,2). This demonstrates the close connection between cancer and inflammation (3). Neuroinflammation and pain are characteristic and fundamental symptoms of the central and peripheral nervous systems. The brain has non-neuronal cells such as glial cells and keratinocytes that play an important role in the pathogenesis of diseases, including cancer. In recent years, much has been learned about the immune response to brain tumors and it has been seen that inflammation plays an important role both in the central nervous system (CNS) (4) and in other areas of the body.

Experimental and clinical studies have shown that tumor development is related to the host's immune response (5,6). In fact, histological analyses of tumor tissue shows the presence of immune cells surrounding the tumor mass (7). Immune cells, such as lymphocytes and monocytes, generate inflammatory cytokines in tumor tissue, including brain tissue (8). The inflammation produced by the excessive production and secretion of pro-inflammatory cytokines promotes the development and progression of tumors.

Received: 02 September, 2017
Accepted: 26 October, 2017

2279-5855 (2017)

DISCUSSION

In brain tumor tissue, there are immune cells such as lymphocytes and monocytes that are recruited to the tumor site in response to new tissue that is recognized as non-self. These immune cells generate cytokines and produce chemokines which attract further immune cells, producing an excess of inflammatory cytokines that exacerbates tumor development (9).

In brain tumors, immune cells, and particularly Th1 cells which physiologically monitor and maintain neuronal integrity, are activated (10). In glioma tumors, microglial cells and macrophages make up approximately 30% of the inflammatory cells in the brain (11). Inflammation in brain tumors manifests with edema (containing inflammatory proteins) which causes an increase in intracranial pressure and compromises the circulation of cerebrospinal fluid (CSF) (12). This phenomenon can give rise to hydrocephalus, resulting in headaches, hypertension, and shock, a life-threatening event. CNS tumors are often accompanied by fever and headache which represent the response to the inflammatory state (13,14).

Immunotherapy is a biological strategy that trains the immune system to recognize tumor neoantigens generated by genetic mutations. The activation of effector T lymphocytes plays an important role in homeostasis and in combating specific antigens, although excessive stimulation can induce an autoimmune phenomenon (15). In tumors, fever is caused by brain inflammation (called sterile inflammation), which should not be confused with fever that is induced by microorganisms. It has been reported that pro-inflammatory cytokines promote tumor cell development and play an important role in brain pathogenesis. Inflammatory cytokines contribute to brain tumor invasion and metastasis through the induction of metalloproteinases (16). In addition, inflammatory cytokines such as IL-1 and tumor necrosis factor (TNF) can have an autocrine effect, aggravating tumorigenic activity (17).

In the brain, proliferative and invasive tumors develop using non-transforming cells and chemoattracting molecules such as chemokines (18). These molecules are a subfamily of cytokines that have the ability to migrate and exert their biological effects through their specific transmembrane receptors (19). They are classified into C, CC, CX3C, and CXC categories based on the cysteine position on their molecular structure (20). The chemokines CCL2 and CXCL8 belong to the CXC subgroup and are produced by glial cells that express their receptors. These chemokines mediate diverse biological effects, including angiogenesis, invasiveness, proliferation, and cell survival (Table I).

Table I. *Some of the biological effects that are mediated by certain chemokines.*

Chemokine	Biological effect
• CXCL1	Reepithelization
• CXCL8	Tissue remodeling
• CXCL10	Inflammation
• CXCL12	Reepithelization, inflammation, angiogenesis
• CCL2	Inflammation, mast cell (MC) chemoattractant
• CCL5	Fibroblast migration
• CCL27	Keratinocyte chemoattractant, effector cell recruitment to sites of epithelial injury
• CCL28	Effector cell recruitment to sites of epithelial injury

Mast cells (MCs) are ubiquitous immune cells that are involved in innate and adaptive immunity. They are classic cells known to mediate allergic diseases and also participate in the development of brain tumors (21). The accumulation of MCs in cancer tissue can have dual effects, as it can be either beneficial or detrimental for the development of tumors.

These cells are present in brain tissue and can generate neuroinflammation that promotes tumor growth (22). Chemokines recruit MCs into brain tumor tissue where they become activated and generate different cytokines such as IL-8, growth factors, and vascular endothelial growth factor (VEGF), chemical mediators such as histamine and heparin, and tryptase and chymase that support the formation of new blood vessels and mediate the production of metastases (21). At the same time, MCs can be detrimental for tumor cells by producing several cytokines, including IL-1, IL-4, IL-6, and TNF, which limit the growth of the tumor mass and the formation of metastasis (23).

CONCLUSIONS

The immune system plays an important role in the brain and in tumors of the CNS. After they are recruited by chemokines released *in situ*, immune cells release inflammatory cytokines that may be beneficial or detrimental to tumor growth and the formation of metastasis.

Current research has focused attention on the use of immunotherapies for treating cancer, including brain tumors. Chimeric antigen receptor (CAR) T-cell therapy utilizes reconstructed patient T-cells that express CAR proteins directed toward surface-exposed tumor-associated antigens (TAAs). The use of CAR T-cell therapy has shown promising results in hematologic cancer studies (24) and for lymphoma (25,26); however, more research is needed to discover the role for this therapy in brain tumors, and for its utilization in clinical practice.

Conflict of interest

The author declares that they have no conflict of interest.

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