European Journal of Neurodegenerative Diseases
ISSN 2279-5855 / 2020 vol. 9, ISSUE N. 2, July-December

Letter to the Editor

HEART FAILURE: ANXIETY, DEPRESSION AND MEMORY IMPAIRMENT

C. D'Ovidio*

Section of Legal Medicine, Department of Medicine and Ageing Sciences, G. D'Annunzio University of Chieti/Pescara, Chieti, Italy.

**Correspondence to*:
Christian D'Ovidio MD,
Section of Legal Medicine,
Department of Medicine and Ageing Sciences,
G.D'Annunzio University of Chieti/Pescara,
Via dei Vestini 21,
66100 Chieti, Italy.
e-mail: cristian.dovidio@unich.it

KEYWORDS: *heart failure, anxiety, depression, memory impairment, cytokine, TNF, inflammation, immunity*

INTRODUCTION

Blood vessels are essential for the regular functioning of cardiac and peripheral circulation, and occlusion can cause heart failure, heart attack and death of the heart muscle (1). Heart disease (failure and myocardial infarction) ranks first in the global fatal cause of all diseases. In addition, systolic heart disease can cause neurological problems with impaired cognition, memory loss, and depression (2). Thus, systolic dysfunction causes decreased cerebral blood flow and a pathological state of the brain with glial activation, oxidative stress, inflammation, and cell death (3).

There is evidence that patients with myocardial infarction have brain impairment; although the cardiac disease does not appear to directly affect cognitive impairment, anxiety, and depression, limited data is available in the literature to date (4). Myocardial infarction leads to heart failure with impaired contractility of the heart muscle, decreased blood flow, and cognitive brain dysfunction. Therefore, reducing cerebral blood flow (CBF) in myocardial infarction impairs cognitive function, including attention span (5).

The main mechanisms leading to neuroinflammation, such as cell death and oxidative stress, are reduced blood flow induced by systemic alteration and inflammation. For example, Angiotensin has two receptors, AT1 and AT2 (7). AT1 is a G protein-coupled receptor that activates phospholipase C and the phosphatidylinositol pathway (8). Its action leads to a general increase in blood pressure due to resistance and cardiac activity. Thus, AT1 receptor dysfunction may also be responsible for neuroinflammation. These effects involve a reduction of oxygen and cerebral nutrients and increasing substances such as reactive oxygen species (ROS) accompanied by synaptic and mitochondrial dysfunction and cell and brain death (9).

Myocardial infarction leads to heart failure with impaired contractility of the heart muscle, decreased blood flow, and cognitive brain dysfunction. These effects involve a reduction of oxygen and cerebral nutrients and increasing substances such as reactive oxygen species (ROS) accompanied by synaptic and mitochondrial dysfunction and cell and brain death (10). In these dynamics, inflammation occurs with the activation of the toll-like receptor4 (TLR4) and pro-inflammatory cytokines such as IL-1, TNF and IL-6. These cytokines are released by activated microglia, which in their physiological state, protect the brain tissue against infections and infectious products (11). After myocardial infarction, microglia are

Received: 23 May, 2020
Accepted: 10 July, 2020

2279-5855 (2020)

activated and contribute to the cognitive disorder. In addition, by producing pro-inflammatory cytokines, heart failure causes dysregulation of membrane phospholipids by releasing phospholipase A2, which activates the arachidonic acid cascade via cyclooxygenases 1 and 2 (12).

These reactions lead to the formation of inflammatory prostaglandins. Moreover, the activation of arachidonic acid causes the release of lipoxygenase with the formation of leukotrienes LTC4, D4 and E4, which contribute to systemic low-grade inflammation and pain (13). Using non-steroidal anti-inflammatory drugs by blocking cyclooxygenase inhibits the formation of prostaglandins and can help against inflammation and pain. Corticosteroids also strongly inhibit the arachidonic acid cascade by inhibiting phospholipase A2 (14) (Fig.1).

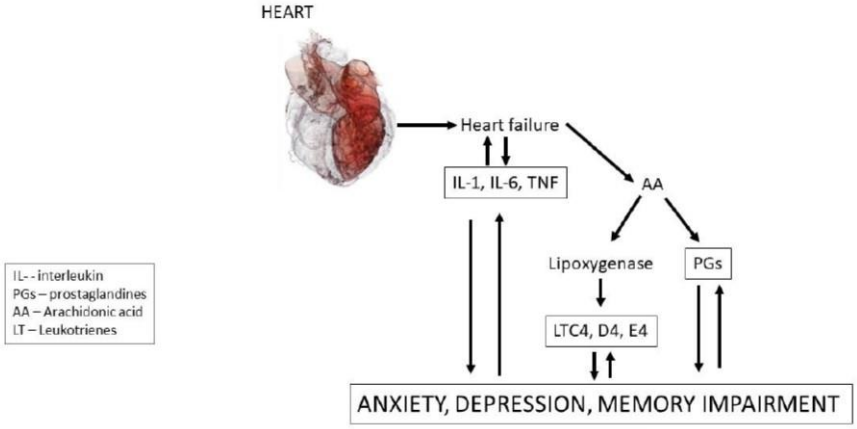

Fig. 1. *Heart failure generates inflammatory cytokines (IL-1, IL-6, and TNF) and activates an arachidonic acid cascade with the production of pro-inflammatory leukotrienes and prostaglandins, which together lead to anxiety, depression and memory impairment. In addition, brain dysfunction (anxiety, depression and memory impairment) can release inflammatory compounds through microglia, which contributes to heart failure.*

IL-1 released by microglia after heart failure and the role in depression

IL-1 was cloned about 30 years ago, and after a few years, caspase-1 was identified, a molecule capable of transforming inactive pro-IL-1 into the biologically active form and activating protein complexes called inflammasomes. The inflammasome consists of a nucleotide oligomerisation domain (NOD)-like receptor (NLR), which consists of an intracellular sensor and adapter protein that recruits pro-caspase with caspase cleavage and activation (15). The NLR comprises 22 receptors, in which NLRP1 and P3 have been characterised; they form the inflammasomes that activate pro-caspase-1, which transitions into the mature form (16). The CNS is a cage where peripheral immune cells cannot enter due to the blood-brain barrier (BBB). This protection can be impaired by pathological brain conditions such as tumors and inflammation. Infiltrating immune cells into the brain generates pro-inflammatory cytokines and microglia activation, producing IL-1, IL-6, and TNF (17).

Since microglia are connected to neurons and cerebral vessels, inflammatory cytokines can influence the physiological state of the brain, causing anxiety, depression and memory impairment. Conversely, it is known that anxiety, depression and memory impairment can activate microglia to produce pro-inflammatory cytokines (18).

Brain inflammation may be related to depression after myocardial infarction with activation of the STAT3 pathway and IL-1 production. In fact, IL-1 and TNF increase in circulation both in depressed patients and in those with myocardial infarction (19).

Neuropeptides bound to their receptors mediate numerous biological effects on the CNS locally and peripherally. For example, some neuropeptides play important roles in regulating systemic blood pressure, memory and anxiety, effects that can be inhibited by specific antagonistic receptors that can have therapeutic effects in hypertension, heart failure, anxiety and depression (20).

In heart failure, brain inflammation caused by IL-1, IL-6, TNF and other pro-inflammatory molecules is responsible for anxiety, depression and memory impairment. Several cells, such as calcium-binding cells CD11b, are increased in the CNS after myocardial infarction, with microglial overactivity, suggesting the close link between heart disease and the brain (21). IL-1, IL-6 and TNF mRNA levels are also upregulated in the CNS. CNS diseases, such as cognitive impairment due to myocardial infarction, often lead to neuron loss and brain cell death leading to cognitive impairment. In this heart

disease, inflammatory genes may increase with the involvement of the amygdala and dysfunction of calcium-binding proteins with cell death. In addition, Bcl-2, a regulator of apoptosis, a mechanism involving caspase, may also be impaired (22).

IL-6

Cells of innate immunity produce IL-6, a cytokine essential for various physiological functions in host defence. IL-6 plays a vascular protective role in heart disease. This cytokine is mainly generated by macrophage cells, fibroblasts, and endothelial cells. IL-6 can be activated by IL-1 during the inflammatory process and, by binding to the IL-6R receptor, forms a complex that binds to the GP130 protein, activating cellular biological effects (23). By blocking IL-6 through inhibition of its IL-6R receptor or gp130, or transcription factors, a valid therapeutic approach can be obtained for inflammatory pathologies, including myocardial infarction. In addition, IL-1 inhibitors, such as IL-37 and IL-38, may also have a valuable therapeutic effect against IL-6-mediated pathologies.

IL-6 inhibition with monoclonal antibodies is still in an experimental phase, and therefore, further studies are needed to clarify their effects (24).

TNF

Inflammatory cytokines participate in the pathophysiology of heart failure. TNF is strongly implicated in the pathogenesis of coronary artery disease, influencing the contractile function of cardiac cells and contributing to the inflammatory process. TNF is an important inflammatory cytokine in heart disease, although there are no studies that blocking TNF does not help patients with heart failure. TNF, in myocardial infarction, can be induced by mechanical action but also by IL-1 and plays a key role in the pathogenesis of the heart muscle and can be generated by different types of cells, such as cardiomyocytes, macrophages, mast cells, vascular cells, fibroblasts, etc. The action of TNF in this pathology can contribute to the patient's death, aggravating the inflammatory network (25).

TNF is part of the inflammatory cascade in activating central and peripheral neuropathic pain, contributing to cell death with memory impairment and neurodegeneration. Therefore, its inhibition could be a viable therapeutic route in subjects with systemic inflammation and cases of neurodegenerative pathologies (26).

CONCLUSIONS

Myocardial infarction may activate microglia and astrocyte remodeling resulting in the production of inflammatory compounds, including cytokines IL-1, IL-6, TNF, prostaglandins, leukotrienes and ROS, demonstrating a close relationship between cardiac disease and brain functions such as anxiety, depression and memory impairment. However, many of these works have been done on rodents, and some authors report conflicting results; therefore, these data should be confirmed by further future studies (27).

Conflict of interest

The author declares that they have no conflict of interest.

REFERENCES

1. Jay Widmer R, Lerman A. Endothelial dysfunction and cardiovascular disease. *Global Cardiology Science and Practice*. 2014;2014(3):43. doi:https://doi.org/10.5339/gcsp.2014.43
2. Leto L, Feola M. Cognitive impairment in heart failure patients. *Journal of Geriatric Cardiology : JGC*. 2014;11(4):316-328. doi:https://doi.org/10.11909/j.issn.1671-5411.2014.04.007
3. de Montgolfier O, Pinçon A, Pouliot P, et al. High Systolic Blood Pressure Induces Cerebral Microvascular Endothelial Dysfunction, Neurovascular Unit Damage, and Cognitive Decline in Mice. *Hypertension*. 2019;73(1):217-228. doi:https://doi.org/10.1161/hypertensionaha.118.12048
4. Celano CM, Villegas AC, Albanese AM, Gaggin HK, Huffman JC. Depression and Anxiety in Heart Failure. *Harvard Review of Psychiatry*. 2018;26(4):175-184. doi:https://doi.org/10.1097/hrp.0000000000000162
5. Izzo C, Carrizzo A, Alfano A, et al. The Impact of Aging on Cardio and Cerebrovascular Diseases. *International Journal of Molecular Sciences*. 2018;19(2). doi:https://doi.org/10.3390/ijms19020481

6. Wang W, Ma X, Han J, et al. Neuroprotective Effect of Scutellarin on Ischemic Cerebral Injury by Down-Regulating the Expression of Angiotensin-Converting Enzyme and AT1 Receptor. Ahmad M, ed. *PLOS ONE*. 2016;11(1):e0146197. doi:https://doi.org/10.1371/journal.pone.0146197
7. Saavedra JM. Angiotensin II AT1 receptor blockers as treatments for inflammatory brain disorders. *Clinical science (London, England : 1979)*. 2012;123(10):567-590. doi:https://doi.org/10.1042/CS20120078
8. Kelley GG, Kaproth-Joslin KA, Reks SE, Smrcka AV, Wojcikiewicz RJH. G-protein-coupled Receptor Agonists Activate Endogenous Phospholipase Cϵ and Phospholipase Cβ3 in a Temporally Distinct Manner. *Journal of Biological Chemistry*. 2006;281(5):2639-2648. doi:https://doi.org/10.1074/jbc.m507681200
9. Akbar M, Essa MM, Daradkeh G, et al. Mitochondrial dysfunction and cell death in neurodegenerative diseases through nitroxidative stress. *Brain Research*. 2016;1637:34-55. doi:https://doi.org/10.1016/j.brainres.2016.02.016
10. Moris D, Spartalis M, Spartalis E, et al. The role of reactive oxygen species in the pathophysiology of cardiovascular diseases and the clinical significance of myocardial redox. *Annals of Translational Medicine*. 2017;5(16). doi:https://doi.org/10.21037/atm.2017.06.27
11. DiSabato DJ, Quan N, Godbout JP. Neuroinflammation: the devil is in the details. *Journal of Neurochemistry*. 2016;139:136-153. doi:https://doi.org/10.1111/jnc.13607
12. Yin P, Wei Y, Wang X, Zhu M, Feng J. Roles of Specialized Pro-Resolving Lipid Mediators in Cerebral Ischemia Reperfusion Injury. *Frontiers in Neurology*. 2018;9. doi:https://doi.org/10.3389/fneur.2018.00617
13. Sonnweber T, Pizzini A, Nairz M, Weiss G, Tancevski I. Arachidonic Acid Metabolites in Cardiovascular and Metabolic Diseases. *International Journal of Molecular Sciences*. 2018;19(11):3285. doi:https://doi.org/10.3390/ijms19113285
14. Allaj V, Guo C, Nie D. Non-steroid anti-inflammatory drugs, prostaglandins, and cancer. *Cell & Bioscience*. 2013;3(1):8. doi:https://doi.org/10.1186/2045-3701-3-8
15. Franchi L, Eigenbrod T, Muñoz-Planillo R, Nuñez G. The inflammasome: a caspase-1-activation platform that regulates immune responses and disease pathogenesis. *Nature Immunology*. 2009;10(3):241-247. doi:https://doi.org/10.1038/ni.1703
16. Tang D, Kang R, Berghe TV, Vandenabeele P, Kroemer G. The molecular machinery of regulated cell death. *Cell Research*. 2019;29(5):347-364. doi:https://doi.org/10.1038/s41422-019-0164-5
17. da Fonseca ACC, Matias D, Garcia C, et al. The impact of microglial activation on blood-brain barrier in brain diseases. *Frontiers in Cellular Neuroscience*. 2014;8. doi:https://doi.org/10.3389/fncel.2014.00362
18. Zhang L, Zhang J, You Z. Switching of the Microglial Activation Phenotype Is a Possible Treatment for Depression Disorder. *Frontiers in Cellular Neuroscience*. 2018;12. doi:https://doi.org/10.3389/fncel.2018.00306
19. Mann DL. Inflammatory Mediators and the Failing Heart. *Circulation Research*. 2002;91(11):988-998. doi:https://doi.org/10.1161/01.res.0000043825.01705.1b
20. Yi M, Li H, Wu Z, et al. A Promising Therapeutic Target for Metabolic Diseases: Neuropeptide Y Receptors in Humans. *Cellular Physiology and Biochemistry*. 2018;45(1):88-107. doi:https://doi.org/10.1159/000486225
21. Cazareth J, Guyon A, Heurteaux C, Chabry J, Petit-Paitel A. Molecular and cellular neuroinflammatory status of mouse brain after systemic lipopolysaccharide challenge: importance of CCR2/CCL2 signaling. *Journal of Neuroinflammation*.2014;11(1). doi:https://doi.org/10.1186/1742-2094-11-132
22. Decourt B, Lahiri D, Sabbagh M. Targeting Tumor Necrosis Factor Alpha for Alzheimer's Disease. *Current Alzheimer Research*. 2016;13(999):1-1. doi:https://doi.org/10.2174/1567205013666160930110551
23. Tanaka T, Narazaki M, Kishimoto T. Interleukin (IL-6) Immunotherapy. *Cold Spring Harbor Perspectives in Biology*. 2017;10(8):a028456. doi:https://doi.org/10.1101/cshperspect.a028456
24. Narazaki M, Kishimoto T. The Two-Faced Cytokine IL-6 in Host Defense and Diseases. *International Journal of Molecular Sciences*. 2018;19(11):3528. doi:https://doi.org/10.3390/ijms19113528
25. Tian M, Yuan YC, Li JY, Gionfriddo MR, Huang RC. Tumor necrosis factor-α and its role as a mediator in myocardial infarction: A brief review. *Chronic Diseases and Translational Medicine*. 2015;1(1):18-26. doi:https://doi.org/10.1016/j.cdtm.2015.02.002
26. Fischer R, Maier O. Interrelation of Oxidative Stress and Inflammation in Neurodegenerative Disease: Role of TNF. *Oxidative Medicine and Cellular Longevity*. 2015;2015:1-18. doi: https://doi.org/10.1155/2015/610813

27. Wang HW, Ahmad M, Jadayel R, Najjar F, Lagace D, Leenen FHH. Inhibition of inflammation by minocycline improves heart failure and depression-like behaviour in rats after myocardial infarction. Bader M, ed. *PLOS ONE*.2019;14(6):e0217437. doi:https://doi.org/10.1371/journal.pone.0217437

European Journal of Neurodegenerative Diseases
ISSN 2279-5855 / 2020 vol. 9, ISSUE N. 2, July-December

THE IMPACT OF ULTRAVIOLET LIGHT ON HISTAMINE RELEASED BY MAST CELLS

I. Frydas*

Aristotelian University, Thessaloniki, Greece.

**Correspondence to*:
Ilias Frydas, MD,
Laboratory of Microbiology and Infectious Diseases,
School of Veterinary Medicine,
Aristotle University of Thessaloniki, Greece.
e-mail: frydas@vet.auth.gr

ABSTRACT

UV irradiation has different effects on the degranulation of mast cells (MCs), and different irradiation intensities are crucial for histamine MC release. In this study, we explored the action of UVC irradiation (with a wavelength range of 240-280 nm) on the degranulation of MCs. After irradiation, two different histamine releasers, compound 48/80 and compound A23187, were used to stimulate noncytotoxic histamine release from rat peritoneal MCs. These compounds activated histamine release, and UVC-irradiation inhibited this effect. Low UVC doses produced stronger and more complete inhibition of the noncytotoxic histamine release from MCs by compound 48/80, and the release induced by the Ca^{2+} ionophore A23187 showed the lowest UVC sensitivity. Our results revealed that the specific mechanisms of MC degranulation are sensitive to UVC irradiation. We believe that the power of UV irradiation is important for the amount of histamine released by MCs and that UVC irradiation could have therapeutic implications and serve as a new experimental tool for the analysis of different mechanisms of MC degranulation.

KEYWORDS: *ultraviolet light, mast cell, histamine, UVC, immunity*

INTRODUCTION

Evidence about the effect of ultraviolet light on mast cells (MCs) has led to the conclusion that UVB irradiation inhibits MC degranulation in a noncytotoxic manner (1). In contrast, UVA irradiation is without detectable effects, even though some authors reported that when irradiation is stronger, there can be stimulation of histamine rather than inhibition (2); This shows that different irradiation intensities are crucial for histamine release by MCs.

On the other hand, UVA is an effective therapeutic mean in combination with the alkylating drug 8-methoxy psoralen [PUVA-therapy (3)]. Until now, as far as we know, no data has been published about the activation of ultraviolet light with a wavelength in the range of 240-280 nm (UVC) on MCs. Due to the absorption spectra of proteins, nucleic acids, and oxygen, UVC-induced biological effects are mainly mediated by the generation of sulfur and tyrosine radicals in proteins, thymine dimerization in nucleic acids, and the effects of singlet oxygen (4).

In this study, the first data is reported about the action of UVC-irradiation on the degranulation of MCs. We compared the influence of two different histamine releasers by UVC on MC degranulation. Since the mechanism of mediator release from MCs is only partially understood, the question arises whether UVC-irradiation might represent a new experimental tool for analysing different mechanisms of MC degranulation.

Received: 06 June, 2020
Accepted: 15 July, 2020

2279-5855 (2020)

MATERIALS AND METHODS

The cell suspensions, obtained from the peritoneal cavity of male Wistar rats (200-250 g), contained 3-5% MCs and were used without further purification. Histamine was determined according to fluorometric analysis (5). All experiments were designed as parallel determinations of the sample's total histamine content, spontaneous histamine efflux during the experiment, and chemically induced histamine release. 4-5 parallel determinations from each sample (containing 11,000 MCs) were carried out.

The irradiation source was used as a low-pressure mercury lamp with a nearly monochromatic emission at 254 nm. In order to prevent light absorption by multi-cell layers, which is of great significance at short wavelength ultraviolet irradiation, and to ensure a randomly distributed irradiation of the whole cell surface, the cell suspension (4 ml) was passed (with different flow rates) through a cuvette (diameter 0.5mm) which was located at a distance of 2 cm from the irradiation source. The intensity of the irradiation was measured with the aid of a commercially available set containing a calibrated cesium/antimony photosensitive unit.

Two different substances were used for the stimulation of noncytotoxic histamine release from the MCs immediately after irradiation:

(a) Compound 48/80, 0.3 μg/sample

(b) A23187, 10^{-6}M

These concentrations represent optimal values which were derived from the corresponding dose-response curves. The Ca^{2+} ionophore A23187 was diluted from a stock solution (10^{-4}M) in dimethyl sulfoxide since it is not directly soluble in aqueous solutions. Control experiments have shown that 1% dimethyl-sulfoxide does not affect the properties of MCs (data not shown).

All data are reported as mean ± SD. Statistical calculations were based on the unpaired student's t-test. P values of <0.05 were considered indicative of statistically significant differences.

RESULTS

In this study, rat peritoneal MCs were activated by two secretagogues, compound 48/80 at 0.3 μg/sample and A23187 at 10^{-6}M, which stimulated histamine release, an effect inhibited by UVC-irradiation. The maximum inhibition was obtained at 1.74 mJ/cm^2, while the initial inhibition began at 0.097 mJ/cm^2 irradiation (Fig.1).

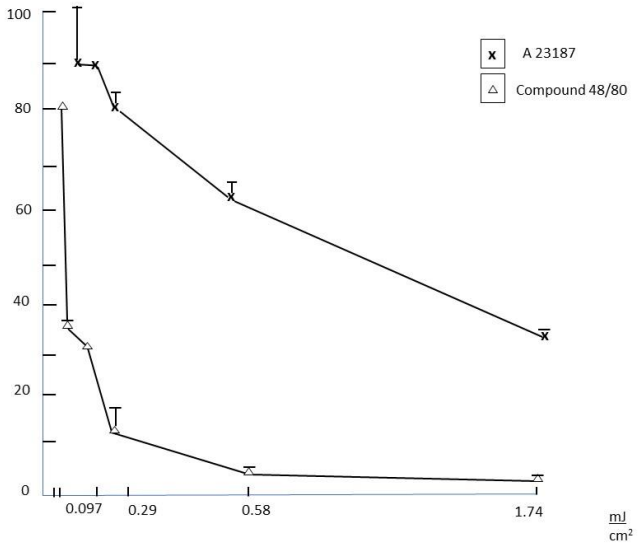

Fig. 1. *UVC inhibition of two different histamine releasors, A23187 and compound 48/80, on rat peritoneal mast cells (MCs.*

Figure 1 shows that low UVC doses resulted in a strong and complete inhibition of the noncytotoxic histamine release from MCs by compound 48/80. The histamine release that the Ca^{2+} ionophore A23187 can induce has the lowest UVC sensitivity, which is documented by the statistical significance of the differences in the effects of UVC irradiation on compound 48/80 induced mediator release.

The UVC-induced effects occur at an irradiation intensity about 1000-fold lower than the UVB, which inhibits the compound 48/80-induced histamine release from rat peritoneal MCs. Contrary to the results obtained with UVB, there is only a slight increase in the spontaneous histamine release at the highest UVC intensities (Fig.2).

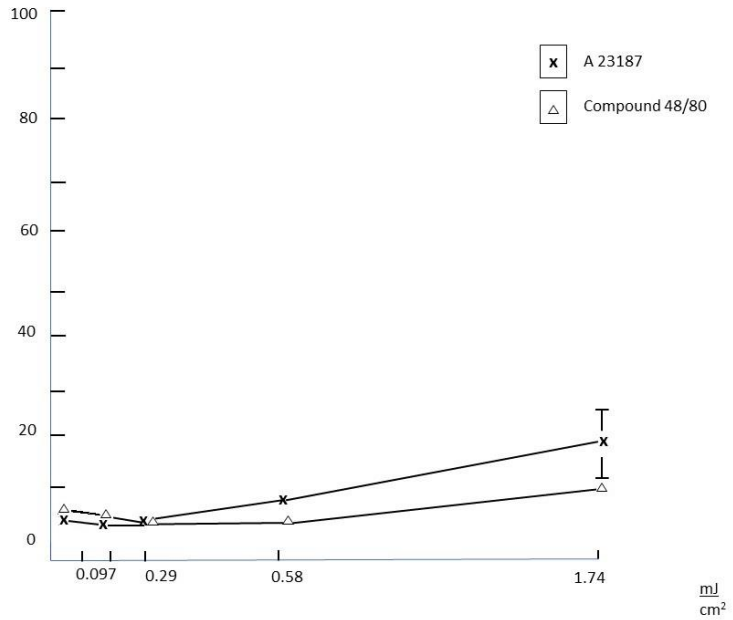

Fig. 2. *Spontaneous histamine release from rat peritoneal MCs after UVC-irradiation in the absence of A23187 and compound 48/80. The data belongs to those cell suspensions used for the histamine release experiments, as shown in Figure 1.*

As shown in Figure 3, UVC slightly reduces the total amount of detectable histamine (Fig.3). This may be due to an unknown chemical modification of the substance under the influence of ultraviolet light. Therefore, all values of the induced or spontaneous histamine release were corrected for the total amount of detectable histamine so that the observed decline of total histamine with increasing UVC doses did not interfere with the data presented in Figures 1 and 2.

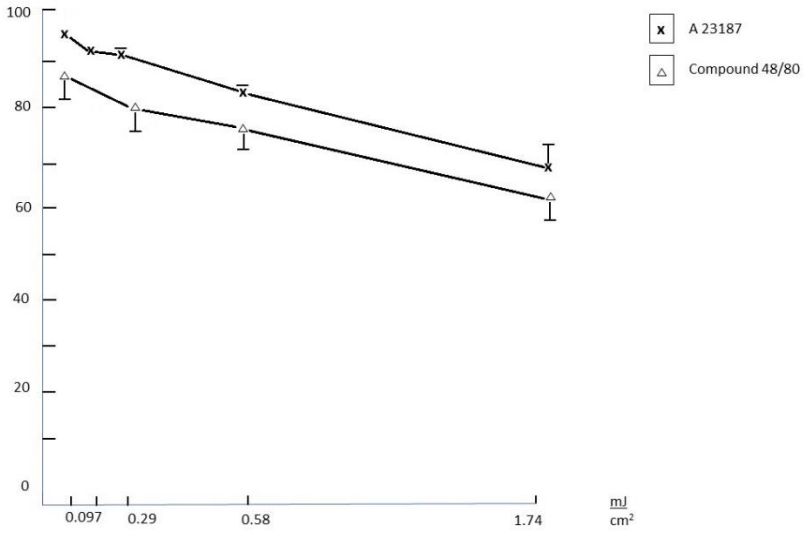

Fig. 3. *Decrease of the amount of detectable total histamine after UVC-irradiation within those cell suspensions used for the histamine release experiments according to Figure 1.*

There was no statistically significant correlation between the percentage of induced histamine release (40-80%) of the total histamine and the inhibitory effect of UVC (data not shown); this indicates that no "spare mechanisms" permit a histamine release that UVC does not influence.

DISCUSSION

The results presented in this paper show that specific mechanisms of MC degranulation are highly sensitive to UVC irradiation (6). The 1,000-fold higher efficiency of UVC compared to the doses of UVB required for comparable effects might be explained by the strong absorption and functional alteration of membrane proteins (7). Furthermore, since the inhibitory effect of UVC can be detected immediately after irradiation, the involvement of nucleic acids is rather unlikely (8).

Due to the larger difference between the inhibitory and the cytotoxic action of UVC (the latter expressed as % spontaneous histamine release) on MCs compared to that of UVB, we suggest reconsideration for the use of small UVC doses for the therapy of *Urticaria pigmentosa*, psoriasis, and anaphylactic skin reactions.

A detailed analysis of the mechanisms of the UVC-induced inhibition of MC degranulation would require a complex biochemical and enzymological analysis. Therefore, we approached this problem in another manner by using two substances which induce histamine release from MCs by different mechanisms and by two different receptors.

The significantly different effects of UVC on the mediator release by 48/80 and A23187 permit the first conclusions. Generally, the induced histamine release by these compounds should be very sensitive to UVC-irradiation if it is completely regulated via enzyme systems located at the cell membrane. However, unlike UVB and UVA, UVC irradiation is almost entirely absorbed by the cell membrane (9).

The above hypothesis seems to be in accordance with the strong inhibition of histamine release by compound 48/80 since the action of this compound is independent of the intracellular cAMP metabolism. However, presumably, it depends on the membrane receptor, the calcium ionophore, and the phospholipid metabolism in the cell membrane (10).

Using the Ca^{2+} ionophore A23187 eliminates the essential role of functioning systems for the opening of the native Ca^{2+} ionophore and seems to reduce the importance of the phosphatidylserine metabolism during MC degranulation; this might explain the low UVC sensitivity of A23187-induced histamine release.

CONCLUSIONS

In this study, we found that A23187 and compound 48/80 activate histamine release, an effect inhibited by UVC irradiation. Of course, these preliminary interpretations of our results are highly speculative. However, on the other hand, the results seem to justify the conclusion that the inhibition of histamine release from MCs by UVC irradiation might be a promising new therapy and approach for the analysis of MC degranulation mechanisms.

Conflict of interest

The author declares that they have no conflict of interest.

REFERENCES

1. Hart PH, Grimbaldeston MA, Swift GJ, Jaksic A, Noonan FP, Finlay-Jones JJ. Dermal Mast Cells Determine Susceptibility to Ultraviolet B–induced Systemic Suppression of Contact Hypersensitivity Responses in Mice. *Journal of Experimental Medicine*. 1998;187(12):2045-2053. doi:https://doi.org/10.1084/jem.187.12.2045
2. Mio M, Yabuta M, Kamei C. Ultraviolet B (UVB) light-induced histamine release from rat peritoneal mast cells and its augmentation by certain phenothiazine compounds. *Immunopharmacology*. 1999;41(1):55-63. doi:https://doi.org/10.1016/s0162-3109(98)00053-8
3. Delrosso G, Savoia P. Effectiveness and Safety of Topical Phototherapy in the Treatment of Dermatological Diseases. *Photomedicine - Advances in Clinical Practice*. Published online May 17, 2017. doi:https://doi.org/10.5772/65712
4. D'Orazio J, Jarrett S, Amaro-Ortiz A, Scott T. UV Radiation and the Skin. *International Journal of Molecular Sciences*. 2013;14(6):12222-12248. doi:https://doi.org/10.3390/ijms140612222

5. Işeri-Erten SÖ, Dikmen ZG, Ulusu NN. Comparison of Spectrophotometric and Fluorimetric Methods in Evaluation of Biotinidase Deficiency. *Journal of Medical Biochemistry*. 2016;35(2):123-129. doi:https://doi.org/10.1515/jomb-2016-0004
6. Siiskonen H, Smorodchenko A, Krause K, Maurer M. Ultraviolet radiation and skin mast cells: Effects, mechanisms and relevance for skin diseases. *Experimental Dermatology*. 2017;27(1):3-8. doi:https://doi.org/10.1111/exd.13402
7. Anna B, Blazej Z, Jacqueline G, Andrew CJ, Jeffrey R, Andrzej S. Mechanism of UV-related carcinogenesis and its contribution to nevi/melanoma. *Expert review of dermatology*. 2007;2(4):451-469. doi:https://doi.org/10.1586/17469872.2.4.451
8. Rastogi RP, Richa, Kumar A, Tyagi MB, Sinha RP. Molecular Mechanisms of Ultraviolet Radiation-Induced DNA Damage and Repair. *Journal of Nucleic Acids*. 2010;2010(592980):1-32. doi:https://doi.org/10.4061/2010/592980
9. Marchitti SA, Chen Y, Thompson DC, Vasiliou V. Ultraviolet Radiation: Cellular Antioxidant Response and the Role of Ocular Aldehyde Dehydrogenase Enzymes. *Eye & Contact Lens: Science & Clinical Practice*. 2011;37(4):206-213. doi:https://doi.org/10.1097/icl.0b013e3182212642
10. Rothschild AM. Mechanisms of histamine release by compound 48/80. *British Journal of Pharmacology*. 1970;38(1):253-262. doi:https://doi.org/10.1111/j.1476-5381.1970.tb10354.x

European Journal of Neurodegenerative Diseases
ISSN 2279-5855 / 2020 vol. 9, ISSUE N. 2, July-December

NERVOUS SYSTEM DISORDERS AND HEADACHE

F. Pandolfi*

Allergy and Clinical Immunology, Fondazione Policlinico Universitario A, Gemelli IRCCS, Catholic University, Rome, Italy.

**Correspondence to*:
Franco Pandolfi,
Allergy and Clinical Immunology,
Fondazione Policlinico Universitario A. Gemelli IRCCS, Catholic University,
00168 Rome, Italy.
e-mail: franco.pandolfi@unicatt.it

ABSTRACT

Neuropathology is the medical science that studies diseases of the nervous system with motility, sensitivity, and balance disorders. The brain can be affected by various disorders, such as stroke, epilepsy, multiple sclerosis, Alzheimer's disease, Parkinson's disease, brain infection, speech disorders, movement disorders, sleep disorders, encephalitis, aphasia, meningitis, and headache, which can affect the entire nervous system, including the spinal cord and nerves. Here in this paper, we will focus our study on headache, which are frequent and debilitating disorders of this medical branch. There are various etiologies of headache, and these diseases are important not only for their pathological severity but also for their emotional and social cost. About 13% of the population in Western countries suffers from headache, affecting more women than men. Various factors can trigger a headache, but in many cases, the reason why an individual has a headache is unknown. Some common foods that can be triggering factors include wine, alcohol, cheese, chocolate, and nuts. Other individuals may be sensitive to cigarette smoke, and headaches can also happen after physical exertion, stress, lack of light, continuous noise and hypertensive states. The characteristic headache is easily identifiable by its symptoms and can be followed by tiredness, vision disturbances, hypersensitivity to light, vomiting and nausea. Some studies report that pro-inflammatory cytokines, such as IL-1, IL-6, and tumor necrosis factor (TNF), are implicated in headache and increase during the acute phase. Headache can be episodic and unilateral and can occur more frequently in patients with asthma and allergies involving immune cells, including central nervous system (CNS) mast cells (MCs). Brain MCs can be activated by neurotransmitters such as substance P (SP) and neurotensin (NT), stimulators of pro-inflammatory cytokines. In addition, brain MCs can produce IL-6 and vascular endothelial growth factor (VEGF) capable of causing vasodilation. This article aims to provide an overview and update on headache and brain disorders.

KEYWORDS: *neuropathology, headache, classification, migraine, cytokine, immune, brain disorder, inflammation*

INTRODUCTION

Neuropathology is the branch of medicine that studies diseases of the nervous system concerning the brain, spinal cord, and nerves. Various pathologies affect the brain, such as stroke, epilepsy, multiple sclerosis, Alzheimer's disease, Parkinson's disease, infections, speech disorders, movement disorders, sleep disorders, encephalitis, aphasia, meningitis, and headaches.

Headaches, including migraine, are a common affliction worldwide responsible for significant disability and have emotional and economic repercussions. Prevalence rates in Western countries are high, with tension-type and general

Received: 25 September, 2020
Accepted: 17 October, 2020

2279-5855 (2020)

headache affecting 60-80% and migraine accounting for 15% of the population, with women affected more frequently than men (1).

There are many different forms of headache, but they are broadly classified into two distinct categories, primary and secondary headaches, classifications defined by The International Classification of Headache Disorders 3rd edition (2). Primary headaches are not caused by another underlying condition and are the most prevalent form of headache experienced in the population. Secondary headaches are a symptom of a separate underlying disease or condition and occur much less frequently than primary headaches, although they can be related to life-threatening diseases. Therefore, headache is a complex disorder that involves both the peripheral and central nervous systems, with the additional involvement of cardiovascular and inflammatory mechanisms.

Types of headaches and their causes

Headache manifests in many forms and can be separated into two major categories: primary and secondary headaches. Primary headaches are disorders caused by independent pathomechanisms (not related to another disease) and account for most cases (about 98%) (3). The main types of primary headaches include migraine, tension-type headache, and trigeminal autonomic cephalalgias, such as cluster headache. These headaches can cause severe pain but are not caused by another underlying condition and, therefore, are not dangerous to the patient's life.

Following tension-type headache, migraine is the second most common type of headache, and it consists of diverse symptoms that are classified into four phases: the premonitory phase, aura phase, acute headache phase, and the postdrome phase that follows the resolution of the headache (4). A migraine is episodic and can last between 4 and 72 hours, and it is characterized by pulsating, throbbing pain, sensitivity to light and sounds, nausea, vomiting, and in many cases, visual disturbances called auras (5).

The pathophysiological basis for migraine is still being investigated, but evidence has suggested that it is caused by vascular and neurogenic mechanisms with the involvement of the immune system (6,7). It is associated with vasodilation, the involvement of serotonin and estrogen, altered brain regions functioning with distinct neuronal activation patterns, activation of the trigeminovascular system, pain sensitization of nociceptors, and an electrophysiological phenomenon of depolarization called cortical spreading depression (5,8).

Many different endogenous or exogenous factors can "trigger" a migraine headache, including stress, physical exertion, hypertensive states, menstruation, changes in weather or sleep, continuous noise, cigarette smoke, and certain foods such as cheeses or processed meats, alcohol (particularly red wine), chocolate, or nuts (9). However, a trigger is often not identifiable, and the reason for the headache is unknown.

Secondary headaches are a symptom of a separate underlying disease or condition that affects pain-sensitivity structures of the head and causes headache. These types of headaches need to be investigated immediately to identify the underlying problem, which can be severe and endanger the life of the sufferer. Many different disorders can cause headache, including the trauma of the head or neck, vascular disorders, epileptic seizures, intracranial infection, and intracranial neoplasms, amongst others (2).

Some common secondary headaches are caused by space-occupying lesions, central nervous system (CNS) infections such as meningitis or encephalitis, subarachnoid haemorrhage, giant-cell arteritis, cerebral venous thrombosis, and idiopathic intracranial hypertension (3).

Although they occur much less frequently, secondary headaches can be life-threatening. Some warning signs associated with secondary headaches include the sudden onset of intense pain, pain and stiffness in the neck, rash, fever, and changes in consciousness related to dangerous conditions.

Headache can cause pain in different areas, and the location of the pain is essential in determining the type of headache and arriving at a diagnosis. Pain can be unilateral, side-shifting, unilateral, bilateral, or unilateral, alternating with bilateral (10). The duration of pain further classifies headaches (lasting less than or more than four hours) and the number of days afflicted by headache (episodic versus chronic) (2).

Immunological aspects of headache

The immune system is also implicated in headache, particularly in migraine, where contributing immunological changes have been established. Neurogenic inflammatory agents are likely involved in the activation and sensitization of peripheral nociceptors, contributing to activation of the trigeminal nerves and inciting the release of vasoactive neuropeptides that contribute to inflammation (7).

Cytokines are immunomodulatory proteins which play an important role in innate and adaptive immunity and are involved in the physiological and pathological mechanisms of neuroinflammation and pain. Studies have shown a link

between pro-inflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor (TNF) (11-13) and headache, with increasing levels during the acute phase of an attack (14).

The action of these pro-inflammatory mediators on peripheral nociceptors is implicated in the sensitization of pain (15) and raised levels of these cytokines have been reported during migraine headache (13,16). The sensitization of nociceptors, partly mediated by inflammation and the immune system, can lead to persistent pain (17). Additionally, intracranial mediators such as nerve growth factor (NGF), Substance P (SP), and calcitonin gene-related peptide (CGRP)could also contribute to primary afferent nociceptor sensitization (18).

Headache can also have a higher rate of frequency in individuals with asthma and allergies, as it involves immune cells such as CNS MCs (19). MCs, derived from hematopoietic pluripotent bone marrow stem cells, migrate to reside near epithelial cells, nerves, and blood vessels. MCs are involved in innate as well as adaptive immune responses and produce and release different inflammatory mediators including cytokines (14).

Migraine occurs with neuroinflammation and involves the innate immune response in the CNS, activating different immune cells such as macrophages, microglia, dendritic cells, and MCs (14). These MCs can be activated by neurotransmitters, including SP and neurotensin (NT) which stimulate the release of pro-inflammatory cytokines and can produce IL-6 and vascular endothelial growth factor (VEGF) which can cause vasodilation.

CONCLUSIONS

Headache is a common and debilitating neuropathology that accounts for disability and economic burden around the world. Primary headaches are the largest types of headache experiences and include tension-type headache, migraine, and cluster headaches. Secondary headaches include those types with a separate, underlying cause in which the headache is a symptom. Often, they are linked with serious, life-threatening disorders, and it is imperative to identify the underlying cause for the health of the patient. In the case of secondary headaches, there is an identifiable cause and if treated, the headache usually subsides as a symptom. In the case of primary headaches, the reason for the headache is often unknown, although certain triggers may exist that bring about onset. These can be endogenous or exogenous factors such as stress, physical exertion, menstruation, changes in weather or sleep, or certain foods. The pathogenic mechanisms that induce primary headaches involve complex interactions between the neurological, vascular, and immune systems. Therefore, more research is still needed to further characterize the origin and nature of these interactions.

Conflict of interest

The author declares that they have no conflict of interest.

REFERENCES

1. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*. 2007;68(5):343-349. doi:10.1212/01.wnl.0000252808.97649.21
2. International Headache Society. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211. doi:10.1177/0333102417738202
3. Ahmed F. Headache disorders: Differentiating and Managing the Common Subtypes. *British Journal of Pain*. 2012;6(3):124-132. doi:10.1177/2049463712459691
4. Charles A. The pathophysiology of migraine: implications for clinical management. *The Lancet Neurology*. 2018;17(2):174-182. doi:10.1016/s1474-4422(17)30435-0
5. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of Migraine: A Disorder of Sensory Processing. *Physiological Reviews*. 2017;97(2):553-622. doi:10.1152/physrev.00034.2015
6. Hoffmann J, Baca SM, Akerman S. Neurovascular mechanisms of migraine and cluster headache. *Journal of Cerebral Blood Flow & Metabolism*. 2019;39(4):573-594. doi:10.1177/0271678X17733655
7. Malhotra R. Understanding migraine: Potential role of neurogenic inflammation. *Annals of Indian Academy of Neurology*. 2016;19(2):175. doi:10.4103/0972-2327.182302
8. Costa C, Tozzi A, Rainero I, et al. Cortical spreading depression as a target for anti-migraine agents. *The Journal of Headache and Pain*. 2013;14(1). doi:10.1186/1129-2377-14-62

9. Kelman L. The triggers or precipitants of the acute migraine attack. *Cephalalgia: an international journal of headache*. 2007;27(5):394-402. doi:10.1111/j.1468-2982.2007.01303.x
10. Prakash S, Rathore C. Side-locked headaches: an algorithm-based approach. *The Journal of Headache and Pain*. 2016;17(1). doi:10.1186/s10194-016-0687-9
11. Zhang X, Burstein R, Levy D. Local action of the pro-inflammatory cytokines IL-1β and IL-6 on intracranial meningeal nociceptors. *Cephalalgia*. 2011;32(1):66-72. doi:10.1177/0333102411430848
12. Martami F, Razeghi Jahromi S, Togha M, Ghorbani Z, Seifishahpar M, Saidpour A. The serum level of inflammatory markers in chronic and episodic migraine: a case-control study. *Neurological Sciences*. 2018;39(10):1741-1749. doi:10.1007/s10072-018-3493-0
13. Sarchielli P, Alberti A, Baldi A, et al. Proinflammatory Cytokines, Adhesion Molecules, and Lymphocyte Integrin Expression in the Internal Jugular Blood of Migraine Patients Without Aura Assessed Ictally. *Headache: The Journal of Head and Face Pain*. 2006;46(2):200-207. doi:10.1111/j.1526-4610.2006.00337.x
14. Conti P, D'Ovidio C, Conti C, et al. Progression in migraine: Role of mast cells and pro-inflammatory and anti-inflammatory cytokines. *European Journal of Pharmacology*. 2019;844:87-94. doi:10.1016/j.ejphar.2018.12.004
15. Obreja O, Schmelz M, Poole S, Kress M. Interleukin-6 in combination with its soluble IL-6 receptor sensitises rat skin nociceptors to heat, in vivo. *Pain*. 2002;96(1):57-62. doi:10.1016/s0304-3959(01)00420-1
16. Zhang XC, Kainz V, Burstein R, Levy D. Tumor necrosis factor-α induces sensitisation of meningeal nociceptors mediated via local COX and p38 MAP kinase actions. *Pain*. 2011;152(1):140-149. doi:10.1016/j.pain.2010.10.002
17. Benemei S, Fusi C, Trevisan G, Geppetti P. The TRPA1 channel in migraine mechanism and treatment. *British Journal of Pharmacology*. 2014;171(10):2552-2567. doi:10.1111/bph.12512
18. Sarchielli P, Alberti A, Floridi A, Gallai V. Levels of nerve growth factor in cerebrospinal fluid of chronic daily headache patients. *Neurology*. 2001;57(1):132-134. doi:10.1212/wnl.57.1.132
19. Okragly AJ, Morin SM, DeRosa D, et al. Human mast cells release the migraine-inducing factor pituitary adenylate cyclase-activating polypeptide (PACAP). *Cephalalgia*. 2017;38(9):1564-1574. doi:10.1177/0333102417740563

European Journal of Neurodegenerative Diseases
ISSN 2279-5855 / 2020 vol. 9, ISSUE N. 2, July-December

TRIGEMINAL NEURALGIA DISORDER: IMMUNITY AND INFLAMMATION

G. Ronconi*

Clinica dei Pazienti del Territorio, Fondazione Policlinico Gemelli, Rome, Italy.

**Correspondence to*:
Dr. Gianpaolo Ronconi,
Clinica dei Pazienti del Territorio,
Fondazione Policlinico Gemelli,
00168 Rome, Italy.
e-mail: gianpaolo.ronconi@policlinicogemelli.it

ABSTRACT

Trigeminal neuralgia (TN) is a chronic neuropathic pain condition that results in unpredictable sporadic, episodic painful sensations in the lower face. The pain occurs suddenly, induced by light vibrations or contact with the face, and is severe, being described as sharp, shooting, and shocking. TN causes great psychological and physical distress for patients and results in lowered quality of life. The etiology and pathology of the disorder are complicated and still unclear. Immunoallergic reactions could contribute to the development of TN, as seen in studies showing higher elevations of IgE and histamine levels in patients, which may involve mast cells. Inflammation occurs in response to trigeminal nerve damage, with an innate immune response involving Schwann cells, mast cells, and macrophages, and the release of cytokines such as TNF, IL-1, MCP-1, and IL-17. An overactive immune response can be negative and result in extreme sensitivity to painful stimuli. Here, the inflammatory reaction that occurs is reviewed in regards to its association with pain sensitivity of the peripheral nervous system in TN disorder.

KEYWORDS: *trigeminal neuralgia disorder, inflammation, immunity, pain, sensitization, neuropathic, cytokine*

INTRODUCTION

Trigeminal neuralgia (TN), also referred to as “tic douloureux”, is the most prevalent form of neuropathic pain and affects the somatosensory system. It is chronic, sporadic, and episodic, and attacks of pain can occur for only a few seconds or for up to 2 minutes. The pain is initiated by non-noxious stimuli, such as touching the face, brushing of teeth, or even a breeze blowing against the face and is localized at the branches of the trigeminal nerve, usually affecting one side of the lower face. The pain is described as shooting or shocking and can be disabling to the patient. The condition is not life-threatening but can cause great stress for sufferers and lower quality of life. TN has a prevalence rate between 0.07 to 0.3% of the population (1, 2) and affects women more frequently than men (3). Treatment to decrease pain is achieved with pharmaceuticals and/or surgery.

The pathogenetic mechanisms of TN are complicated, and its etiology is unclear. Different theories exist to explain both, and studies are showing the involvement of inflammation in the development and physiological processes of TN. The disorder could be caused by neurovascular compression of the trigeminal nerve, but could also result from trauma, inflammation, tumour, or another medical condition, including multiple sclerosis. People with multiple sclerosis (MS), a chronic inflammatory disorder that affects the central nervous system (CNS), have a much higher prevalence of TN, with co-occurrence of 3.8% (4).

Received: 28 September, 2020
Accepted: 12 November, 2020

2279-5855 (2020)

Inflammatory mechanisms are involved in TN and increasing evidence has begun to indicate the role of inflammation (5-7). The sensory nervous system is affected by immune processes and inflammation can cause nociceptive pain. However, the etiopathology of neuropathic pain is complex and not fully understood. It can occur as a result of disease or lesion, and it may be induced by excessive inflammation after nerve damage. In this paper, the role of immunity and inflammation in TN will be explored.

Peripheral nerve trauma, neuropathic pain, and inflammation

The most apparent cause of TN is mechanical distortion at the trigeminal nerve root entrance to the brainstem, where compression is seen with demyelination at the area of root entry (8). This is supported by magnetic resonance imaging (MRI) findings that have shown microstructural changes in the root area of the trigeminal nerve in the presence of compression (9-11). However, a neurovascular conflict is not always present in all cases (12), and it can exist asymptomatically without causing TN (13). After peripheral nerve trauma, an inflammatory response is activated to repair nerve damage. But an excessive inflammatory reaction can lead to long-term pain sensitivity and neuronal changes (14).

Schwann cells (SCs) are myelinating cells of the peripheral nervous system. They are activated after trigeminal nerve damage and convert to a repair cell phenotype, secreting neurotrophic factors including brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin 3 and 4/5, in addition to producing extracellular matrix proteins (15). SC activation leads to down-regulation of myelin genes and up-regulation of trophic factors, myelin sheath destruction, pain sensitivity, and the innate immune response including the release of cytokines (16,17).

SCs interact with immune cells for nerve regeneration. After peripheral nerve damage, axons activate the extracellular signal-related mitogen-activated protein kinase (MAPK) signaling pathway in SCs, triggering the recruitment of immune cells, such as macrophages and MCs, which produce inflammatory cytokines and chemokines, such as tumor necrosis factor (TNF), interleukin 1 (IL-1), and monocyte chemotactic protein 1 (MCP-1) (17-19).

Half of the damaged myelin sheath of the trigeminal nerve is initially cleared by SCs (20), followed by macrophages which phagocytose remaining myelin debris (21,22). MC activation releases inflammatory mediators including histamine, serotonin, leukotrienes, and NGF. These mediators can cause sensitization of nociceptors as well as neutrophil aggregation to the damaged nerve site (23,24). The activation of neutrophils subsequently stimulates macrophages and T cells. T-helper cells release proinflammatory cytokines including IL-1β, TNF, and interleukin 17 (IL-17) (25) (Fig. 1).

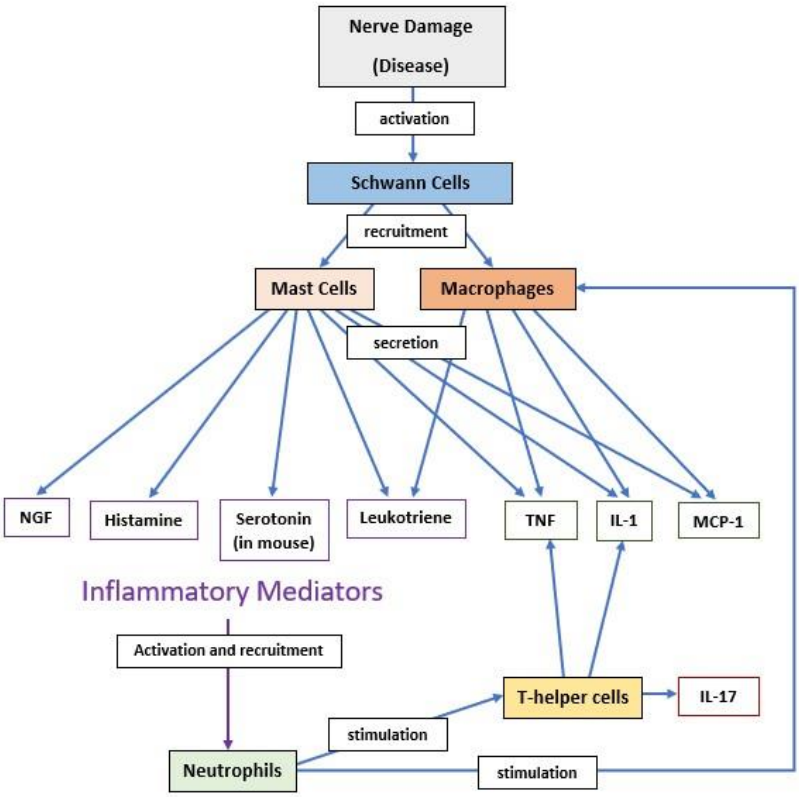

Fig. 1. *Damage to the trigeminal nerve activates Schwann cells, which recruit macrophages and mast cells. These macrophages and mast cells release inflammatory mediators such as TNF, IL-1, MCP-1, histamine, serotonin, leukotrienes, and nerve growth factor, the latter of which cause neutrophil activation and recruitment to the damaged site. The activation of neutrophils subsequently stimulates macrophages and T-helper cells. T-helper cells release proinflammatory cytokines including IL-1, TNF, and IL-17.*

Neutrophil infiltration, and the mediators released afterward by macrophages and T cells, can be linked to the development of hyperalgesia, the extreme sensitivity to painful stimuli (23,26). It was also observed that after nerve damage, hyperalgesia was reduced by macrophage depletion via intravenous injection of liposome-encapsulated clodronate (27), demonstrating the importance of macrophages in this disorder.

In one recent, interesting study it was observed that there were changes in immunological protein levels in cerebrospinal fluid of TN patients before and after treatment of microvascular decompression surgery (28). They found that levels of inflammatory protein markers decreased after surgery to a level that was consistent with a group of healthy controls, and identified two particular proteins of interest, TRAIL, and TNF, that may be involved in inflammation in TN (28).

The peripheral immune response following nerve injury involves the release of mediators that can affect pain sensitivity and could cause changes in the electrophysiological properties of neighboring neurons, leading to long-term neuropathic pain (14,29).

Inflammatory mediators can indirectly affect nociceptors, as cytokine receptors are expressed on sensory neurons. Hyperexcitability of the neural network in neuropathic pain can be caused by changes in ion channel function and nociceptive neuronal activity. Abnormal ion channel functioning leads to spinal and brain sensory signaling changes, which can result in increased neurotransmitter release and excitatory synaptic transmission of nociceptive channels (30). These nociceptor inputs cause central sensitization, producing hypersensitivity to pain, pressure hyperalgesia, and heightened temporal summation, and secondary changes that are produced can be seen by imaging (31).

Inflammation as the origin TN

The etiopathology of TN is unknown, but inflammation may be involved, and different theories exist to support this. Odontogenic inflammatory diseases could be one cause (32,33) and TN development could result from chronic inflammation of maxillary sinuses and inflammatory disorders of the ear, nose, and throat, such as sinusitis, periodontitis, phlegmon, periostitis, and dental cysts (34,35).

Immunoallergic reactions may play a role in the development of TN, as IgE and histamine have been implicated in studies (36-39). Histamine has been proposed to play a key role, as increased serum levels of histamine have been observed in TN patients. Degranulating MCs release mediators, including histamine and serotonin, producing a local hyperergic reaction (40), a process initiated with IgE attachment to MCs in the trigeminal nerve area (41). During the acute period of TN, blood and saliva levels of histamine were found to be raised (42). However, other factors may be responsible for an immune response and the increased IgE and histamine levels observed in TN patients. Therefore, further studies are needed to provide evidence for the allergy hypothesis of TN etiology.

CONCLUSIONS

TN is a chronic neuropathic pain disorder that significantly impacts the quality of life for sufferers, who show higher levels of pain, anxiety, and depression (43). In TN, demyelination occurs at the trigeminal nerve root entry area to the brainstem, and inflammation occurs to repair nerve damage. An exaggerated inflammatory reaction can have effects on central nervous system sensitization, leading to long-term pain sensitivity. An interaction between SCs and immune cells such as macrophages and MCs results in the release of cytokines, chemokines, and other inflammatory mediators, such as histamine. These mediators cause sensitization of nociceptors, contributing to the development of pain hypersensitivity and hyperalgesia.

More research focusing on the role of inflammation in TN should continue, as it could provide therapeutic opportunities. Controlling and containing the extent of inflammation could prevent central nervous system sensitization, therefore limiting pain and improving the outcome for patients.

Conflict of interest

The author declares that they have no conflict of interest.

REFERENCES

1. MacDonald BK. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. *Brain*. 2000;123(4):665-676. doi:10.1093/brain/123.4.665
2. Mueller D, Obermann M, Yoon MS, et al. Prevalence of trigeminal neuralgia and persistent idiopathic facial pain: A population-based study. *Cephalalgia*. 2011;31(15):1542-1548. doi:10.1177/0333102411424619
3. Ibrahim S. Trigeminal neuralgia: diagnostic criteria, clinical aspects and treatment outcomes. A retrospective study. *Gerodontology*. 2012;31(2):89-94. doi:10.1111/ger.12011
4. Fallata A, Salter A, Tyry T, Cutter GR, Marrie RA. Trigeminal Neuralgia Commonly Precedes the Diagnosis of Multiple Sclerosis. *International Journal of MS Care*. 2017;19(5):240-246. doi:10.7224/1537-2073.2016-065
5. Dieb W, Hafidi A. Astrocytes are Involved in Trigeminal Dynamic Mechanical Allodynia. *Journal of Dental Research*. 2013;92(9):808-813. doi:10.1177/0022034513498898
6. Shibuta K, Suzuki I, Shinoda M, et al. Organization of hyperactive microglial cells in trigeminal spinal subnucleus caudalis and upper cervical spinal cord associated with orofacial neuropathic pain. *Brain Research*. 2012;1451:74-86. doi:10.1016/j.brainres.2012.02.023
7. Yao Y, Chang B, Li S. Relationship of Inflammation With Trigeminal Neuralgia. *Journal of Craniofacial Surgery*. 2020;31(2):e110-e113. doi:10.1097/scs.0000000000005879
8. Campbell JN, Meyer RA. Mechanisms of Neuropathic Pain. *Neuron*. 2006;52(1):77-92. doi:10.1016/j.neuron.2006.09.021
9. Leal PRL, Roch JA, Hermier M, Souza MAN, Cristino-Filho G, Sindou M. Structural abnormalities of the trigeminal root revealed by diffusion tensor imaging in patients with trigeminal neuralgia caused by neurovascular compression: A prospective, double-blind, controlled study. *Pain*. 2011;152(10):2357-2364. doi:10.1016/j.pain.2011.06.029
10. Herweh C, Kress B, Rasche D, et al. Loss of anisotropy in trigeminal neuralgia revealed by diffusion tensor imaging. *Neurology*. 2007;68(10):776-778. doi:10.1212/01.wnl.0000256340.16766.1d

11. Liu Y, Li J, Butzkueven H, et al. Microstructural abnormalities in the trigeminal nerves of patients with trigeminal neuralgia revealed by multiple diffusion metrics. *European Journal of Radiology*. 2013;82(5):783-786. doi:10.1016/j.ejrad.2012.11.027
12. Lutz J, Thon N, Stahl R, et al. Microstructural alterations in trigeminal neuralgia determined by diffusion tensor imaging are independent of symptom duration, severity, and type of neurovascular conflict. *Journal of Neurosurgery*. 2016;124(3):823-830. doi:10.3171/2015.2.jns142587
13. Lin W, Chen Y, Zhang Q. Vascular compression of the trigeminal nerve in asymptomatic individuals: a voxel-wise analysis of axial and radial diffusivity. *Acta Neurochirurgica*. 2014;156(3):577-580. doi:10.1007/s00701-013-1970-z
14. Ellis A, Bennett DLH. Neuroinflammation and the generation of neuropathic pain. *British Journal of Anaesthesia*. 2013;111(1):26-37. doi:10.1093/bja/aet128
15. Li Z, Liang Y, Pan K, et al. Schwann cells secrete extracellular vesicles to promote and maintain the proliferation and multipotency of hDPCs. *Cell Proliferation*. 2017;50(4):e12353. doi:10.1111/cpr.12353
16. Ko PY, Yang CC, Kuo YL, et al. Schwann-Cell Autophagy, Functional Recovery, and Scar Reduction After Peripheral Nerve Repair. *Journal of Molecular Neuroscience*. 2018;64(4):601-610. doi:10.1007/s12031-018-1056-8
17. Jessen KR, Mirsky R. The repair Schwann cell and its function in regenerating nerves. *The Journal of Physiology*. 2016;594(13):3521-3531. doi:10.1113/jp270874
18. Martini R, Fischer S, López-Vales R, David S. Interactions between Schwann cells and macrophages in injury and inherited demyelinating disease. *Glia*. 2008;56(14):1566-1577. doi:10.1002/glia.20766
19. Rotshenker S. Wallerian degeneration: the innate-immune response to traumatic nerve injury. *Journal of Neuroinflammation*. 2011;8(1):109. doi:10.1186/1742-2094-8-109
20. Perry VH, Tsao JW, Feam S, Brown MC. Radiation-induced Reductions in Macrophage Recruitment Have Only Slight Effects on Myelin Degeneration in Sectioned Peripheral Nerves of Mice. *European Journal of Neuroscience*. 1995;7(2):271-280. doi:10.1111/j.1460-9568.1995.tb01063.x
21. Vargas ME, Watanabe J, Singh SJ, Robinson WH, Barres BA. Endogenous antibodies promote rapid myelin clearance and effective axon regeneration after nerve injury. *Proceedings of the National Academy of Sciences*. 2010;107(26):11993-11998. doi:10.1073/pnas.1001948107
22. Dubový P, Jančálek R, Kubek T. Role of Inflammation and Cytokines in Peripheral Nerve Regeneration. *International Review of Neurobiology*. 2013;108:173-206. doi:10.1016/b978-0-12-410499-0.00007-1
23. Zuo Y, Perkins NM, Tracey DJ, Geczy CL. Inflammation and hyperalgesia induced by nerve injury in the rat: a key role of mast cells. *Pain*. 2003;105(3):467-479. doi:10.1016/s0304-3959(03)00261-6
24. Smith FM, Haskelberg H, Tracey DJ, Moalem-Taylor G. Role of Histamine H3 and H4 Receptors in Mechanical Hyperalgesia following Peripheral Nerve Injury. *Neuroimmunomodulation*. 2007;14(6):317-325. doi:10.1159/000125048
25. Palmer MT, Weaver CT. Autoimmunity: increasing suspects in the CD4+ T cell lineup. *Nature Immunology*. 2009;11(1):36-40.doi:10.1038/ni.1802
26. Kumar V, Sharma A. Neutrophils: Cinderella of innate immune system. *International Immunopharmacology*. 2010;10(11):1325-1334. doi:10.1016/j.intimp.2010.08.012
27. Liu T, van Rooijen N, Tracey DJ. Depletion of macrophages reduces axonal degeneration and hyperalgesia following nerve injury. *Pain*. 2000;86(1):25-32. doi:10.1016/s0304-3959(99)00306-1
28. Ericson H, Abu Hamdeh S, Freyhult E, et al. Cerebrospinal fluid biomarkers of inflammation in trigeminal neuralgia patients operated with microvascular decompression. *Pain*. 2019;160(11):2603-2611. doi:10.1097/j.pain.0000000000001649
29. Ma C, Shu Y, Zheng Z, et al. Similar Electrophysiological Changes in Axotomized and Neighboring Intact Dorsal Root Ganglion Neurons. *Journal of Neurophysiology*. 2003;89(3):1588-1602. doi:10.1152/jn.00855.2002
30. Colloca L, Ludman T, Bouhassira D, et al. Neuropathic pain. *Nature Reviews Disease Primers*. 2017;3(1). doi:10.1038/nrdp.2017.2
31. Woolf CJ. Central sensitization: Implications for the diagnosis and treatment of pain. *Pain*. 2011;152(Supplement):S2-S15. doi:10.1016/j.pain.2010.09.030
32. Roberts AM, Person P, Chandran NB, Hori JM. Further observations on dental parameters of trigeminal and atypical facial neuralgias. *Oral Surgery, Oral Medicine, Oral Pathology*. 1984;58(2):121-129. doi:10.1016/0030-4220(84)90123-3

33. Francica F, Brickman J, LoMonaco CJ, Lin LM. Trigeminal neuralgia and endodontically treated teeth. *Journal of Endodontics*. 1988;14(7):360-362. doi:10.1016/s0099-2399(88)80199-7
34. Sawaya RA. Trigeminal Neuralgia Associated with Sinusitis. *ORL*. 2000;62(3):160-163. doi:10.1159/000027738
35. Sabalys G, Juodzbalys G, Wang HL. Aetiology and Pathogenesis of Trigeminal Neuralgia: a Comprehensive Review. *Journal of Oral and Maxillofacial Research*. 2012;3(4). doi:10.5037/jomr.2012.3402
36. J.Hanes W. Clinical research on the etiology and treatment of tic douloureux on an allergic basis. *Oral Surgery, Oral Medicine, Oral Pathology*. 1967;23(6):728-736. doi:10.1016/0030-4220(67)90361-1
37. Obara I, Telezhkin V, Alrashdi I, Chazot PL. Histamine, histamine receptors, and neuropathic pain relief. *British Journal of Pharmacology*. Published online June 7, 2019:1-20. doi:10.1111/bph.14696
38. Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. *The Lancet Neurology*. 2010;9(8):807-819. doi:10.1016/s1474-4422(10)70143-5
39. Dobaczewski, Z. "Leczenie histamina nerwobólu nerwu trójdzielnego" [Histamine in the treatment of trigeminal neuralgia]. *Polski tygodnik lekarski* (Warsaw, Poland). 1972;27(24): 913-5.
40. White JR, Pearce FL. Effect of anti-allergic compounds on anaphylactic histamine secretion from rat peritoneal mast cells in the presence and absence of exogenous calcium. *Immunology.* 1982 Jun;46(2):361-7.
41. Chen XJ, Enerbäck L. Regulation of IgE-receptor expression, IgE occupancy and secretory capacity of mast cells. Revie warticle. *APMIS*. 2000;108(10):633-641. doi:10.1034/j.1600-0463.2000.d01-9.x
42. Sabalis, GI et al. "Perifericheskie mekhanizmy patogeneza nevralgii troĭnichnogo nerva" [Peripheral mechanisms of the pathogenesis of trigeminal neuralgia]. Zhurnal nevropatologii i psikhiatrii imeni S.S. Korsakova (Moscow, Russia)1982;82(4):25-9.
43. Hilgenberg-Sydney PB, Calles BM, Conti PCR. Quality of life in chronic trigeminal neuralgia patients. *Revista Dor*. 2015;16(3). doi:10.5935/1806-0013.20150039

European Journal of Neurodegenerative Diseases
ISSN 2279-5855 / 2020 vol. 9, ISSUE N. 2, July-December

THE PATHOGENESIS OF NEUROTRAUMA: IMMUNITY AND INFLAMMATION

D. Lauritano*

Department of Medicine and Surgery, Centre of Neuroscience of Milan, University of Milano-Bicocca, Milan, Italy.

**Correspondence to*:
Dorina Lauritano,
Department of Medicine and Surgery,
Centre of Neuroscience of Milan,
University of Milano-Bicocca,
Milan, Italy.
email: dorina.lauritano@unimib.it

ABSTRACT

Neurotrauma is a serious medical issue, and the mechanisms underlying this pathology are still being studied. It is known that while damaged tissues such as muscles and skin heal without any physiological dysfunction, neurotraumas do not heal properly and undergo functional alterations. Brain injury leads to a neuronal deficit, and the response to glial cell injury involves tissue repair and strengthening in the central nervous system (CNS). In neurotrauma such as spinal cord injury (SCI), various cells are activated, including astrocytes, pericytes, fibroblasts, and Schwann cells, which contribute to glial cell growth and promote fibrotic scarring. Phagocytic cells also participate in the injury by releasing pro-inflammatory cytokines and activating adhesion molecules. Immune cells such as monocytes and neutrophils infiltrate the lesion and mediate inflammation by producing cytokines and chemokines. The neuroinflammation mediated by pro-inflammatory cytokines represents a crucial point of this brain trauma. In this inflammation, where microglia participate, producing pro-inflammatory cytokines and chemokines, endothelial cells are activated with the upregulation of selectins and adhesion molecules. In this complex mechanism, macrophages intervene and contribute to tissue repair and healing. The innate immune response leads to the alteration of the NLRP3 inflammasome with tissue damage and neurological disorders, topics that will be covered here in this paper.

KEYWORDS: *neurotrauma, brain injury, spinal cord injury, central nervous system, neurodegeneration, inflammation, immunity*

INTRODUCTION

Neurotrauma is a sudden injury to the central nervous system (CNS) that includes traumatic brain injury (TBI) and spinal cord injury (SCI). It is a prevalent cause of morbidity and mortality worldwide in the population of individuals aged 45 years and younger (1), with the leading cause being falls and motor vehicle accidents (2).

The injury consists of a sudden, traumatic blow to the brain or spine. SCI involves damage to the spinal cord, resulting in temporary or permanent functional changes. TBI occurs from an external mechanical force to the head that results in an intracranial injury, with damage to the structure or functioning of the brain (3). TBIs are classified based on level of severity and mechanism of injury, but even a minor non-concussive event has the capacity to produce long-term effects (4).

Received: 02 October, 2020
Accepted: 11 November, 2020

2279-5855 (2020)

Following the damage induced by the primary injury to the CNS, a secondary pathological injury occurs that causes an inflammatory response, which can help to repair and regenerate neurons or can exacerbate neurodegeneration (5). The immune response during this secondary injury process is critical in determining the direction of healing, as it can be beneficial and restorative for tissue repair or create further damage with a prolonged and overactive state of inflammation.

The pathophysiological mechanism of neurotrauma

Damaged tissue such as muscle and skin are generally followed by a healthy tissue repair response through a process involving inflammation, angiogenesis, matrix deposition, and cell recruitment, which allows for healing without physiological dysfunction (6). Neurotraumas differ, as they do not heal properly and undergo functional alterations with structural and chemical disruptions and altered metabolic functioning of neurons (7). The pathophysiological mechanisms accompanying biomechanical injury and tissue damage are still being studied, but growing evidence implicates the role of the immune system in the response and repair process that follows neurotrauma (8-10).

Neurotrauma is associated with increased permeability of the blood-brain barrier (BBB), altered axonal transport, and disrupted functions of neuronal and glial cells (11). The primary, mechanical cerebral injury of TBI results in direct tissue damage and impaired metabolic regulation that can be described as an 'ischemia-like' pattern, which results in lactic acid accumulation due to anaerobic glycolysis and increased membrane permeability and subsequent depolarization and the release of neurotransmitters and other compounds that disrupt intracellular processes (1). Structural changes affecting the biological membranes and nucleosome DNA take place, and cellular structures are degraded with subsequent cell death (12).

After the initial, primary brain injury, there are a series of complex pathophysiological mechanisms that take place, a reaction that is termed the "secondary injury". These two events, the primary and secondary injuries, cause neuropathology.

Brain injury results in neuronal damage and primary cell death in the CNS, and the secondary injury can lead to further neuron death, depending on factors such as metabolic and trophic processes and gene transcription (13). The secondary injury involves changes in the CNS including increased or decreased blood perfusion, dysfunction of cerebrovascular autoregulation, loss of oxygenation, metabolic dysfunction, and cell death resulting from inflammation (1).

A continued state of inflammation that is mediated by microglia can continue the secondary injury and can result in chronic neuroinflammation and the progression and development of neurodegenerative disorders (14).

Secondary injury in neurotrauma: an inflammatory cascade

The damaging mechanical forces of neurotrauma results in tissue damage, disrupted CNS homeostasis, and neuronal cell death. This is followed by a cascade of cellular responses that can be reparative or cause secondary cellular injury.

Following a neurotrauma such as SCI, a neuronal deficit activates the immune response in the CNS of tissue repair and strengthening and axon regeneration. Various glial cells such as astrocytes, pericytes, fibroblasts, endothelial cells, and Schwann cells are activated, which contributes to glial cell growth and promotes fibrotic scarring (15). Glial cells serve supportive functions for neurons by modulating synaptic interactions, providing structural support, and aiding, or sometimes preventing, neuronal recovery following neurotrauma (16).

With sudden injury to the CNS, there is axon damage to neurons which interferes with cell signaling with the loss of synaptic connections and propagation, and cell death (17). Glial cells release toxins and cytokines in response to the mechanical damage of the injury, which can go on to damage surrounding remaining tissue that was not mechanically injured by the initial trauma (15). Signaling cascades ensue with the infiltration of nonresident cells. Successively, fibroblasts are activated and inhibitory extracellular matrix (ECM) proteins such as chondroitin sulfate proteoglycans (CSPGs) are generated that prevent axon growth (18).

Following this, the secondary injury ensues with further disruption to neuronal functioning. These primary and secondary injuries result in activated glial cells and the formation of cellular scars at the injury site of the spinal cord. The fibrotic scar is largely composed of collagen, fibronectin, and laminin deposits in the core of the lesion (17).

Phagocytic cells also participate in the injury. Monocytes and macrophages detect damaged tissues via damage-associated molecular patterns (DAMPs) and when they are activated, they release anti-inflammatory molecules and neurotrophic factors, beneficial for tissue regeneration, but also secrete pro-inflammatory cytokines which can exacerbate secondary injury (19). Studies of monocyte and macrophage processes have revealed that M1 macrophages participate in inflammation by cytokine release and tissue degeneration, while M2 macrophages contribute to neuronal repair and healing (20).

This innate immune response leads to alterations of the NLRP3 inflammasome, which is involved in the physiopathology of diverse neurological disorders such as Alzheimer's disease, Parkinson's disease, and multiple

sclerosis (21). The induction of NLRP3 leads to cleavage of caspase-1 and the maturation of IL-1, which is released and recruits further immune cells from the ECM, adding to inflammation and tissue damage (21,22).

Microglia are innate immune cells ubiquitous throughout the CNS that act similarly to macrophage cells. They are quick to respond following brain and spinal cord injury and play a vital role in the reparation process (23). They react swiftly to neurotrauma by releasing pro-inflammatory mediators that recruit other inflammatory cells including neutrophils and monocytes (24). Monocytes, glial cells, and neutrophils, which detect damaged tissue and promote the breakdown and clearance of debris at the injury site, release pro-inflammatory mediators with the activation of endothelial cells and the upregulation of selectins and adhesion molecules. Secondary damage is inflicted with the release of inflammatory cytokines IL-1, IL-6, and tumor necrosis factor (TNF) (25-27).

CONCLUSIONS

With brain trauma, neuroinflammation is mediated by pro-inflammatory cytokines (28). In TBI, If the microglial response subsides after neuronal repair and homeostasis is restored, the secondary injury period is neuroprotective. But continual microglial activation in the CNS and an exaggerated, chronic state of inflammation is damaging to neurons. This harmful inflammatory reaction can cause neuronal dysfunction and interfere with gene suppression and lead to neurological disorders.

CNS axon regeneration with glial cells is now being targeted as a focus of therapeutic efforts in neurotrauma, as damaged cells are involved in scar formation and an ensuing inflammatory process that prevents neuronal axon growth (29).

In conclusion, the immune response is vital to neurological tissue repair and regeneration after neurotrauma, but also can cause a harmful inflammatory response that contributes to neuronal death and neurodegeneration.

Conflict of interest

The author declares that they have no conflict of interest.

REFERENCES

1. Werner C, Engelhard K. Pathophysiology of traumatic brain injury. *British Journal of Anaesthesia*. 2017;99(1):4-9. doi:https://doi.org/10.1093/bja/aem131
2. Langlois JA, Rutland-Brown W, Wald MM. The Epidemiology and Impact of Traumatic Brain Injury. *Journal of Head Trauma Rehabilitation*. 2006;21(5):375-378. doi:https://doi.org/10.1097/00001199-200609000-00001
3. Fehily B, Fitzgerald M. Repeated Mild Traumatic Brain Injury. *Cell Transplantation*. 2017;26(7):1131-1155. doi:https://doi.org/10.1177/0963689717714092
4. Makinde HM, Just TB, Cuda CM, Perlman H, Schwulst SJ. The Role of Microglia in the Etiology and Evolution of Chronic Traumatic Encephalopathy. *Shock (Augusta, Ga)*. 2017;48(3):276-283. doi:https://doi.org/10.1097/SHK.0000000000000859
5. Ray S, Dixon CE, Banik NL. Molecular mechanisms in the pathogenesis of traumatic brain injury. *Histology and histopathology*. 2002;17(4):1137-52. doi:https://doi.org/10.14670/HH-17.1137
6. Eming SA, Martin P, Tomic-Canic M. Wound repair and regeneration: Mechanisms, signaling, and translation. *Science Translational Medicine*. 2014;6(265):265sr6-265sr6. doi:https://doi.org/10.1126/scitranslmed.3009337
7. Solstrand Dahlberg L, Becerra L, Borsook D, Linnman C. Brain changes after spinal cord injury, a quantitative meta-analysis and review. *Neuroscience & Biobehavioral Reviews*. 2018;90:272-293. doi:https://doi.org/10.1016/j.neubiorev.2018.04.018
8. McKee CA, Lukens JR. Emerging Roles for the Immune System in Traumatic Brain Injury. *Frontiers in Immunology*. 2016;7. doi:https://doi.org/10.3389/fimmu.2016.00556
9. Balu R. Inflammation and Immune System Activation After Traumatic Brain Injury. *Current Neurology and Neuroscience Reports*. 2014;14(10). doi:https://doi.org/10.1007/s11910-014-0484-2
10. Plesnila N. The immune system in traumatic brain injury. *Current Opinion in Pharmacology*. 2016;26:110-117. doi:https://doi.org/10.1016/j.coph.2015.10.008

11. Chodobski A, Zink BJ, Szmydynger-Chodobska J. Blood–Brain Barrier Pathophysiology in Traumatic Brain Injury. *Translational Stroke Research*. 2011;2(4):492-516. doi:https://doi.org/10.1007/s12975-011-0125-x
12. Miller MA, Zachary JF. Mechanisms and Morphology of Cellular Injury, Adaptation, and Death11For a glossary of abbreviations and terms used in this chapter see E-Glossary 1-1. *Pathologic Basis of Veterinary Disease*. Published online 2017:2-43.e19. doi:https://doi.org/10.1016/b978-0-323-35775-3.00001-1
13. Kermer P, Klöcker N, Bähr M. Neuronal death after brain injury. *Cell and Tissue Research*. 1999;298(3):383-395. doi:https://doi.org/10.1007/s004410050061
14. Faden AI, Wu J, Stoica BA, Loane DJ. Progressive inflammation-mediated neurodegeneration after traumatic brain or spinal cord injury. *British Journal of Pharmacology*. 2015;173(4):681-691. doi:https://doi.org/10.1111/bph.13179
15. Gaudet AD, Fonken LK. Glial Cells Shape Pathology and Repair After Spinal Cord Injury. *Neurotherapeutics*. 2018;15(3):554-577. doi:https://doi.org/10.1007/s13311-018-0630-7
16. Kou Z, VandeVord PJ. Traumatic white matter injury and glial activation: From basic science to clinics. *Glia*. 2014;62(11):1831-1855. doi:https://doi.org/10.1002/glia.22690
17. Orr MB, Gensel JC. Spinal Cord Injury Scarring and Inflammation: Therapies Targeting Glial and Inflammatory Responses. *Neurotherapeutics*. 2018;15(3):541-553. doi:https://doi.org/10.1007/s13311-018-0631-6
18. Jones LL, Sajed D, Tuszynski MH. Axonal Regeneration through Regions of Chondroitin Sulfate Proteoglycan Deposition after Spinal Cord Injury: A Balance of Permissiveness and Inhibition. *The Journal of Neuroscience*. 2003;23(28):9276-9288. doi:https://doi.org/10.1523/jneurosci.23-28-09276.2003
19. Popovich PG, Guan Z, McGaughy V, Fisher L, Hickey WF, Basso DM. The Neuropathological and Behavioral Consequences of Intraspinal Microglial/Macrophage Activation. *Journal of Neuropathology & Experimental Neurology*. 2002;61(7):623-633. doi:https://doi.org/10.1093/jnen/61.7.623
20. David S, Kroner A. Repertoire of microglial and macrophage responses after spinal cord injury. *Nature Reviews Neuroscience*. 2011;12(7):388-399. doi:https://doi.org/10.1038/nrn3053
21. Eren E, Özören N. The NLRP3 inflammasome: a new player in neurological diseases. *Turkish Journal Of Biology*. 2019;43(6):349-359. doi:https://doi.org/10.3906/biy-1909-31
22. Jorgensen I, Lopez JP, Laufer SA, Miao EA. IL-1β, IL-18, and eicosanoids promote neutrophil recruitment to pore-induced intracellular traps following pyroptosis. *European Journal of Immunology*. 2016;46(12):2761-2766. doi:https://doi.org/10.1002/eji.201646647
23. Perry VH, Teeling J. Microglia and macrophages of the central nervous system: the contribution of microglia priming and systemic inflammation to chronic neurodegeneration. *Seminars in Immunopathology*. 2013;35(5):601-612. doi:https://doi.org/10.1007/s00281-013-0382-8
24. Loane DJ, Byrnes KR. Role of microglia in neurotrauma. *Neurotherapeutics*. 2010;7(4):366-377. doi:https://doi.org/10.1016/j.nurt.2010.07.002
25. Pineau I, Lacroix S. Proinflammatory cytokine synthesis in the injured mouse spinal cord: Multiphasic expression pattern and identification of the cell types involved. *The Journal of Comparative Neurology*. 2006;500(2):267-285. doi:https://doi.org/10.1002/cne.21149
26. Lawrence CB, Allan SM, Rothwell NJ. Interleukin-1β and the interleukin-1 receptor antagonist act in the striatum to modify excitotoxic brain damage in the rat. *European Journal of Neuroscience*. 1998;10(3):1188-1195. doi:https://doi.org/10.1046/j.1460-9568.1998.00136.x
27. Ferguson AR, Christensen RN, Gensel JC, et al. Cell Death after Spinal Cord Injury Is Exacerbated by Rapid TNF -Induced Trafficking of GluR2-Lacking AMPARs to the Plasma Membrane. *Journal of Neuroscience*. 2008;28(44):11391-11400. doi:https://doi.org/10.1523/jneurosci.3708-08.2008
28. Kempuraj D, Ahmed ME, Selvakumar GP, et al. Brain Injury–Mediated Neuroinflammatory Response and Alzheimer's Disease. *The Neuroscientist*. 2019;26(2):134-155. doi:https://doi.org/10.1177/1073858419848293
29. Sami A, Selzer ME, Li S. Advances in the Signaling Pathways Downstream of Glial-Scar Axon Growth Inhibitors. *Frontiers in Cellular Neuroscience*. 2020;14. doi:https://doi.org/10.3389/fncel.2020.00174

European Journal of Neurodegenerative Diseases
ISSN 2279-5855 / 2020 vol. 9, ISSUE N. 2, July-December

ROLE OF INFLAMMATION IN ALZHEIMER'S DISEASE: AN EMPHASIS ON TREM2 AND CD33

Al. Caraffa*

School of Pharmacy, University of Camerino, Camerino, Italy.

**Correspondence to*:
Alessandro Caraffa,
School of Pharmacy,
University of Camerino,
Camerino, Italy.
e-mail: alecaraffa@libero.it

ABSTRACT

Alzheimer's disease (AD) is the leading cause of dementia globally. It is a progressive and irreversible neurologic disorder that results in personality changes, memory loss, cognitive decline, and death. Hallmarks of the disease include extracellular amyloid-β (Aβ) plaque deposition, the accumulation of neurofibrillary tangles (NFTs) of hyperphosphorylated tau, and neuroinflammation. Aβ plaque deposition is believed to be central to the pathogenesis of AD. Activation of microglia, innate immune cells of the central nervous system, can have both beneficial and harmful consequences, as they are able to aid in Aβ plaque clearance, but also release damaging pro-inflammatory cytokines. Microglial cells are involved with Aβ plaque formations and may play a central role in AD pathogenesis. Diverse gene networks implicating microglia and affecting immune function have been identified, including microglial receptors triggering receptors expressed on myeloid cells 2 (TREM2) and CD33. Both are considerable risk factors for the development of late-onset AD and in this paper, we summarize their role, and that of microglia, in the inflammation occurring in AD.

KEYWORDS: *Alzheimer's disease, inflammation, immunity, TREM2, CD33, microglia, neurology, neurodegenerative*

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurologic disorder and the leading cause of dementia worldwide (1). Most cases are late-onset, usually occurring after the age of 65 (2). It is characterized by extracellular amyloid-β (Aβ) plaque deposition and the accumulation of neurofibrillary tangles (NFTs) of hyperphosphorylated tau. Symptoms include memory loss, changes in personality and behavior, progressive cognitive decline, and eventually, death. Genetic changes can cause AD to an extent.

AD is complex, but different theories exist to explain the mechanisms involved. The most predominant is the Aβ cascade hypothesis, focusing on Aβ accumulation as the fundamental element in AD development (3). It theorizes that Aβ groups form plaques on the outside of brain neurons, followed by inflammation and NFTs of tau protein, eventually leading to neuronal death, which then results in neurodegeneration. Evidence has suggested that the inability to clear Aβ is central to AD pathogenesis, rather than the overproduction of Aβ (4).

Neuroinflammation is another hallmark of AD, with elevated expression of inflammatory mediators, and microglia and astrocytes showing changes in morphology, activation, and distribution (5, 6). Microglia are innate immune cells resident in the central nervous system (CNS), responsible for immune surveillance and mediation. They are important for

Received: 03 October, 2020
Accepted: 27 December, 2020
2279-5855 (2020)

tissue repair and damage control, but their response can also be detrimental to the release of pro-inflammatory substances. It is believed that inflammation mediated by microglia plays a central role in the progression of AD, but the process is complex and the exact mechanisms by which this occurs is still unclear.

CD33 and triggering receptor expressed on myeloid cells 2 (TREM2) are microglial receptors that regulate inflammation in AD and are associated risk factors. In this paper we summarize the pathogenesis of late onset AD with a focus on the role of microglia in inflammation and the involvement of CD33 and TREM2.

Microglial cells

In the brain, microglia have functions similar to macrophages, providing immune surveillance and tissue maintenance. Microglial cells and Aβ formation is linked. Microglia protect the CNS by helping to clear Aβ plaque formations, yet fibrillar Aβ can activate microglia, leading to the release of inflammatory mediators, such as pro-inflammatory cytokines, that can be damaging to the CNS (7).

Microglia are plastic, with the ability to change phenotype in response to stimuli and interact with neurons to mediate the immune environment (8). They show branching dynamics, the capability to expand and retract into neighboring tissue, which allows for continuous immune surveillance and rapid convergence to an injury site (9). This includes the response to Aβ plaque that occurs with AD.

Aβ plaque formation can activate microglia to an inflammatory phenotype, as seen in animal models (10,11). Microglia congregate to Aβ deposits, mostly converging at the sites of densely concentrated plaques, with fewer observed in unconcentrated surrounding areas (12,13). Microglia are attracted to plaque, congregating around formations, and increasing and growing over time (14-16).

Surface cell receptor and toll-like receptor (TLR)-detection of intracellular proteins and damage-associated molecular patterns (DAMP) molecules initiate the innate immune response to injury. Interestingly, increased expression of CD14 (17), TLR2, and TLR4 (18) by microglia has been seen in the AD brain (19).

In the AD brain, deposition of fibrillar forms of Aβ occurs, activating microglia through a cell surface receptor complex that includes the B-class scavenger receptor CD36, the integrin-associated protein/CD47, and the α6β1-integrin (20). This leads to signaling cascades, and the defensive reaction of activated microglia includes the production of free radicals and the release of pro-inflammatory cytokines that can contribute to CNS injury. The inflammation that occurs is thought to be integral in the progression of the disease. In fact, microglial activation in AD brains has been associated with elevated levels of cytokines and chemokines, such as interferon γ (IFNγ), tumor necrosis factor (TNF), interleukin 1β (IL-1β), interleukin 6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1) (21-24).

In their role as principal immune effectors, microglia participate in phagocytosis, removing and clearing targets such as pathogens, apoptotic cells, and cellular debris. Microglia can internalize fibrillar forms of Aβ, but degradation and complete clearance is not always effective (25-27). Diverse studies have shown that inflammation may negatively interfere with the ability of microglial cells to clear Aβ plaques (28-30).

Additionally, microglia cell surface receptors are important for Aβ recognition and subsequent response (31). Microglia require the triggering receptor TREM2 for the phagocytosis of certain substrates, including Aβ (32). TREM2-deficient microglia were seen to remain inactivated and not congregate around Aβ plaques (33,34) (Fig.1).

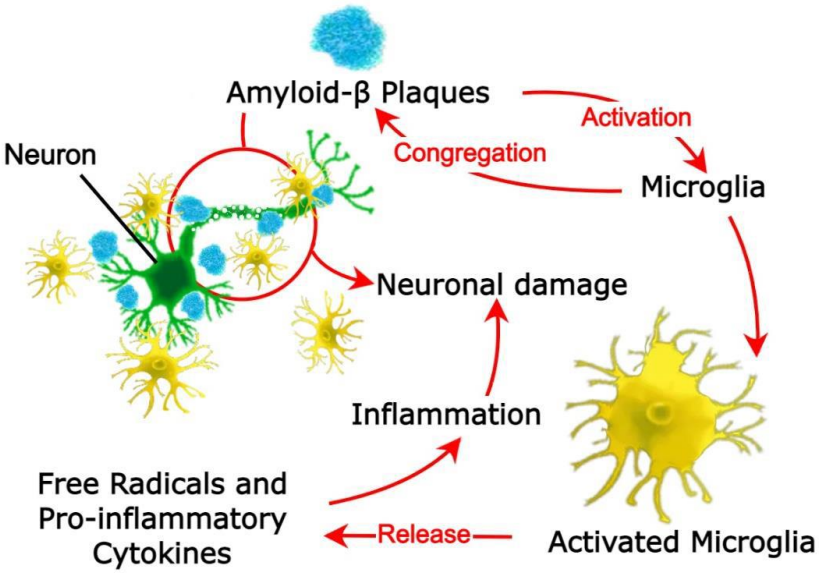

Fig. 1. *Amyloid-β (Aß) groups to form plaques on the outside of brain neurons, causing neuronal damage. Aß plaque deposition activates microglial cells, which congregate to sites of Aß plaque formation and release free radicals and pro-inflammatory cytokines, leading to inflammation and subsequent neuronal damage.*

Genetic risk factors

Heritability for late onset AD is high, does not differ by sex, and is estimated to be between 58-79% in twin studies (35). Apolipoprotein E ε4 (APOE ε4) was the first confirmed genetic risk factor (36), until recently when many different genes have been identified to be associated with the development of AD, numerous of which are also associated with inflammation and microglia (37). Some of these gene networks that are closely tied to the immune system, such as CR1, SPI1, the MS4As, TREM2, ABCA7, CD33, and INPP5D, are expressed by microglia (37). This supports the role that neuroinflammation plays in the development of AD.

Microglial receptors TREM2 and CD33, which are involved in immune function activation and are associated with one another, are of particular interest in AD. CD33 is one of the top-ranked genes for risk of AD and is exclusively expressed in microglia. Rare variants of TREM2 are a considerable risk factor and can increase the risk of developing AD by 2-4 times (5).

CD33

CD33 is a transmembrane myeloid cell receptor that is expressed in microglia and macrophages in the brain, with the ability to inhibit immune cell functions. In genome-wide association studies, CD33 has been identified as one of the greatest risk factors for AD (38-40), with two variants posing the highest risk, rs3865444 and rs12459419 (41,42).

Studies have suggested that CD33 is involved in diverse immune functions, including cell adhesion processes, endocytosis, immune cell growth, TLR4 signaling, and can inhibit the release of cytokines (43-45).

It is believed that its expression regulates the activation of microglia and interferes with the clearance of Aβ by inhibition, with Aβ plaque formation resulting in turn (46). CD33 is increased in the brain with AD, correlated with disease severity as well as the extent of Aβ plaque formation (47). The T allele of single-nucleotide polymorphism (SNP) rs3865444 has been associated with decreased CD33 levels and Aβ plaque burden in the brain (45), and the C allele was associated with increased CD33 levels and Aβ plaque burden (48).

Evidence shows that CD33 may inhibit the production of pro-inflammatory cytokines such as IL-1β, TNF, IL-8, and furthermore, increased TNF secretion by immune cells was seen with the downregulation of CD33 (49). Animal studies have also revealed evidence, as mice without CD33 showed greatly reduced Aβ plaque levels (45).

Because CD33 inhibits Aβ clearance, subsequently generating the formation of Aβ plaques, targeting CD33 could be a therapeutic opportunity in AD.

TREM2

TREM2 is a triggering receptor expressed on myeloid cells, and microglia are responsible for TREM2 expression in the CNS, where it is associated with inflammation (5). It can suppress the production of pro-inflammatory cytokines and promote phagocytosis of Aβ plaque by microglia (50,51).

TREM2 expression is increased by the expression of anti-inflammatory molecules, while pro-inflammatory ones, such as TNF and IL-1β, decrease its expression (51,52). Microglial aggregation to Aβ plaques causes upregulation of TREM2, which has been reported in animal models and humans (53,54). TREM2 upregulation is also associated with aging (55).

TREM2 binds to Aβ, is involved in microglial activation and degradation of Aβ, and mediates the microglial expression of cytokines (56). TREM2 expression promotes phagocytosis by microglia, which has been seen in studies correlating increased expression with increased phagocytosis (50,57), and decreased phagocytosis with TREM2 loss (58,59). TREM2 moderates microglial functions and binds to Aβ, and mutations of TREM2 in AD reduce Aβ binding (56). TREM2 also modulates inflammation by signaling and has anti-inflammatory effects (50), although some studies seem to show an association with pro-inflammatory effects as well (60,61). Lastly, TREM2 affects the proliferation and survival of myeloid cells, including microglia (59).

TREM2 variants are a significant risk factor for late-onset AD. Rs75932628 is a common TREM2 gene variant risk factor. It has been identified in European and North American populations in diverse studies but cannot be confirmed in Chinese communities (62-65).

CONCLUSIONS

AD is a prevalent and highly complex neurodegenerative disorder. Increasing evidence suggests that inflammation plays a vital role in the development of the pathogenesis of the disease. Aβ plaque deposition is thought to be a fundamental characteristic of AD. The inability to effectively clear Aβ plaque formations is likely the key to disease progression, rather than Aβ overproduction. Microglia and Aβ are closely associated, with the formation of Aβ plaques activating microglia and causing microglial congregation. Microglia aid in phagocytosis and clearance of Aβ but can also release harmful pro-inflammatory cytokines.

Heritability is high and diverse genes have been identified that implicate microglia and immune function in the development of AD. Microglial receptors CD33 and TREM2 are involved in immune function and are two significant risk factors for AD development.

Conflict of interest

The author declares that they have no conflict of interest.

REFERENCES

1. Prince M, Wimo A, Ali GC, et al. *World Alzheimer Report 2015 the Global Impact of Dementia an analysis of prevalence, incidence, cost and trends Dr Maëlenn Guerchet Alzheimer's Disease International*.; 2015. Accessed September 29, 2019. http://www.alzheimer.it/report2015.pdf
2. Holtzman DM, Morris JC, Goate AM. Alzheimer's Disease: The Challenge of the Second Century. *Science Translational Medicine*. 2011;3(77):77sr1-77sr1. doi:10.1126/scitranslmed.3002369
3. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science (New York, NY)*. 2002;297(5580):353-356. doi:10.1126/science.1072994
4. Mawuenyega KG, Sigurdson W, Ovod V, et al. Decreased Clearance of CNS -Amyloid in Alzheimer's Disease. *Science*. 2010;330(6012):1774-1774. doi:10.1126/science.1197623
5. Gratuze M, Leyns CEG, Holtzman DM. New insights into the role of TREM2 in Alzheimer's disease. *Molecular Neurodegeneration*. 2018;13(1). doi:10.1186/s13024-018-0298-9
6. Itagaki S, McGreer P, Akiyama H, Zhu S, Selkoe D. Relationship of microglia and astrocytes to amyloid deposits of Alzheimer disease. *Journal of Neuroimmunology*. 1989;24(3):173-182. doi:10.1016/0165-5728(89)90115-x
7. Cameron B, Landreth GE. Inflammation, microglia, and alzheimer's disease. *Neurobiology of Disease*. 2010;37(3):503-509. doi:10.1016/j.nbd.2009.10.006

8. Colton CA. Heterogeneity of Microglial Activation in the Innate Immune Response in the Brain. *Journal of Neuroimmune Pharmacology*. 2009;4(4):399-418. doi:10.1007/s11481-009-9164-4
9. Davalos D, Grutzendler J, Yang G, et al. ATP mediates rapid microglial response to local brain injury in vivo. *Nature Neuroscience*. 2005;8(6):752-758. doi:10.1038/nn1472
10. Yan P, Bero AW, Cirrito JR, et al. Characterizing the Appearance and Growth of Amyloid Plaques in APP/PS1 Mice. *Journal of Neuroscience*. 2009;29(34):10706-10714. doi:10.1523/jneurosci.2637-09.2009
11. Bornemann KD, Wiederhold KH, Pauli C, et al. Aβ-Induced Inflammatory Processes in Microglia Cells of APP23Transgenic Mice. *The American Journal of Pathology*. 2001;158(1):63-73. doi:10.1016/s0002-9440(10)63945-4
12. Stalder M, Phinney A, Probst A, Sommer B, Staufenbiel M, Jucker M. Association of Microglia with Amyloid Plaques in Brains of APP23 Transgenic Mice. *The American Journal of Pathology*. 1999;154(6):1673-1684. doi:10.1016/s0002-9440(10)65423-5
13. Akiyama H, Mori H, Saido T, Kondo H, Ikeda K, McGeer PL. Occurrence of the diffuse amyloid beta-protein (Abeta) deposits with numerous Abeta-containing glial cells in the cerebral cortex of patients with Alzheimer's disease. *Glia*.1999;25(4):324–331.
14. Wegiel J. The role of microglial cells and astrocytes in fibrillar plaque evolution in transgenic APPSW mice. *Neurobiology of Aging*. 2001;22(1):49-61. doi:10.1016/s0197-4580(00)00181-0
15. Sasaki A, Shoji M, Harigaya Y, et al. Amyloid cored plaques in Tg2576 transgenic mice are characterized by giant plaques, slightly activated microglia, and the lack of paired helical filament-typed, dystrophic neurites. *Virchows Archiv*.2002;441(4):358-367. doi:10.1007/s00428-002-0643-8
16. Meyer-Luehmann M, Spires-Jones TL, Prada C, et al. Rapid appearance and local toxicity of amyloid-beta plaques in a mouse model of Alzheimer's disease. *Nature*. 2008;451(7179):720-724. doi:10.1038/nature06616
17. Liu Y, Walter S, Stagi M, et al. LPS receptor (CD14): a receptor for phagocytosis of Alzheimer's amyloid peptide. *Brain*. 2005;128(8):1778-1789. doi:10.1093/brain/awh531
18. Walter S, Letiembre M, Liu Y, et al. Role of the Toll-Like Receptor 4 in Neuroinflammation in Alzheimer's Disease. *Cellular Physiology and Biochemistry*. 2007;20(6):947-956. doi:10.1159/000110455
19. Letiembre M, Liu Y, Walter S, et al. Screening of innate immune receptors in neurodegenerative diseases: A similar pattern. *Neurobiology of Aging*. 2009;30(5):759-768. doi:10.1016/j.neurobiolaging.2007.08.018
20. Bamberger ME, Harris ME, McDonald DR, Husemann J, Landreth GE. A Cell Surface Receptor Complex for Fibrillarβ-Amyloid Mediates Microglial Activation. *The Journal of Neuroscience*. 2003;23(7):2665-2674. doi:10.1523/jneurosci.23-07-02665.2003
21. T. Griffin WS, Sheng JG, Roberts GW, Mrak RE. Interleukin-1 Expression in Different Plaque Types in Alzheimer's Disease. *Journal of Neuropathology and Experimental Neurology*. 1995;54(2):276-281. doi:10.1097/00005072-199503000-00014
22. Dickson DW, Lee SC, Mattiace LA, Yen SHC, Brosnan C. Microglia and cytokines in neurological disease, with special reference to AIDS and Alzheimer's disease. *Glia*. 1993;7(1):75-83. doi:10.1002/glia.440070113
23. Akiyama H, Barger S, Barnum S, et al. Inflammation and Alzheimer's disease. *Neurobiology of aging*. 2000;21(3):383-421. doi:10.1016/s0197-4580(00)00124-x
24. Ishizuka K, Kimura T, Igata-yi R, Katsuragi S, Takamatsu J, Miyakawa T. Identification of monocyte chemoattractant protein-1 in senile plaques and reactive microglia of Alzheimer's disease. *Psychiatry and Clinical Neurosciences*. 1997;51(3):135-138. doi:10.1111/j.1440-1819.1997.tb02375.x
25. Paresce DM, Chung H, Maxfield FR. Slow Degradation of Aggregates of the Alzheimer's Disease Amyloid β-Protein by Microglial Cells. *Journal of Biological Chemistry*. 1997;272(46):29390-29397. doi:10.1074/jbc.272.46.29390
26. Chung H, Brazil MI, Soe TT, Maxfield FR. Uptake, Degradation, and Release of Fibrillar and Soluble Forms of Alzheimer's Amyloid β-Peptide by Microglial Cells. *Journal of Biological Chemistry*. 1999;274(45):32301-32308. doi:10.1074/jbc.274.45.32301
27. Grathwohl S, Kälin RE, Bolmont T, et al. Formation and maintenance of Alzheimer's disease beta-amyloid plaques in the absence of microglia. *e-Neuroforum*. 2010;16(1):164-167. doi:10.1515/nf-2010-0107
28. Zelcer N, Khanlou N, Clare R, et al. Attenuation of neuroinflammation and Alzheimer's disease pathology by liver x receptors. *Proceedings of the National Academy of Sciences*. 2007;104(25):10601-10606. doi:10.1073/pnas.0701096104

29. Yamamoto M, Kiyota T, Walsh SM, Liu J, Kipnis J, Ikezu T. Cytokine-Mediated Inhibition of Fibrillar Amyloid-βPeptide Degradation by Human Mononuclear Phagocytes. *The Journal of Immunology*. 2008;181(6):3877-3886. doi:10.4049/jimmunol.181.6.3877
30. Koenigsknecht-Talboo J. Microglial Phagocytosis Induced by Fibrillar -Amyloid and IgGs Are Differentially Regulated by Proinflammatory Cytokines. *Journal of Neuroscience*. 2005;25(36):8240-8249. doi:10.1523/jneurosci.1808-05.2005
31. Mandrekar-Colucci S, Landreth GE. Microglia and Inflammation in Alzheimers Disease. *CNS & Neurological Disorders - Drug Targets*. 2010;9(2):156-167. doi:10.2174/187152710791012071
32. Kleinberger G, Yamanishi Y, Suárez-Calvet M, et al. TREM2 mutations implicated in neurodegeneration impair cell surface transport and phagocytosis. *Science Translational Medicine*. 2014;6(243). doi:10.1126/scitranslmed.3009093
33. Jay TR, Miller CM, Cheng PJ, et al. TREM2 deficiency eliminates TREM2+ inflammatory macrophages and ameliorates pathology in Alzheimer's disease mouse models. *Journal of Experimental Medicine*. 2015;212(3):287-295. doi:10.1084/jem.20142322
34. Mazaheri F, Snaidero N, Kleinberger G, et al. TREM2 deficiency impairs chemotaxis and microglial responses to neuronal injury. *EMBO Reports*. 2017;18(7):1186-1198. doi:10.15252/embr.201743922
35. Gatz M, Reynolds CA, Fratiglioni L, et al. Role of Genes and Environments for Explaining Alzheimer Disease. *Archives of General Psychiatry*. 2006;63(2):168. doi:10.1001/archpsyc.63.2.168
36. Schmechel DE, Saunders AM, Strittmatter WJ, et al. Increased amyloid beta-peptide deposition in cerebral cortex as a consequence of apolipoprotein E genotype in late-onset Alzheimer disease. *Proceedings of the National Academy of Sciences*. 1993;90(20):9649-9653. doi:10.1073/pnas.90.20.9649
37. Efthymiou AG, Goate AM. Late onset Alzheimer's disease genetics implicates microglial pathways in disease risk. *Molecular Neurodegeneration*. 2017;12(1). doi:10.1186/s13024-017-0184-x
38. Lambert JC, Ibrahim-Verbaas CA, Harold D, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nature Genetics*. 2013;45(12):1452-1458. doi:10.1038/ng.2802
39. Naj AC, Jun G, Beecham GW, et al. Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. *Nature Genetics*. 2011;43(5):436-441. doi:10.1038/ng.801
40. Cukier HN, Kunkle BK, Hamilton KL, et al. Exome Sequencing of Extended Families with Alzheimer's Disease Identifies Novel Genes Implicated in Cell Immunity and Neuronal Function. *Journal of Alzheimer's Disease & Parkinsonism*. 2017;07(04). doi:10.4172/2161-0460.1000355
41. Malik M, Simpson JF, Parikh I, et al. CD33 Alzheimer's Risk-Altering Polymorphism, CD33 Expression, and Exon 2 Splicing. *Journal of Neuroscience*. 2013;33(33):13320-13325. doi:10.1523/jneurosci.1224-13.2013
42. Bertram L, Lange C, Mullin K, et al. Genome-wide Association Analysis Reveals Putative Alzheimer's Disease Susceptibility Loci in Addition to APOE. *The American Journal of Human Genetics*. 2008;83(5):623-632. doi:10.1016/j.ajhg.2008.10.008
43. Crocker PR, Paulson JC, Varki A. Siglecs and their roles in the immune system. *Nature Reviews Immunology*. 2007;7(4):255-266. doi:10.1038/nri2056
44. Ishida A, Akita K, Mori Y, et al. Negative Regulation of Toll-like Receptor-4 Signaling through the Binding of Glycosylphosphatidylinositol-anchored Glycoprotein, CD14, with the Sialic Acid-binding Lectin, CD33. *Journal of Biological Chemistry*. 2014;289(36):25341-25350. doi:10.1074/jbc.m113.523480
45. Griciuc A, Serrano-Pozo A, Parrado Antonio R, et al. Alzheimer's Disease Risk Gene CD33 Inhibits Microglial Uptake of Amyloid Beta. *Neuron*. 2013;78(4):631-643. doi:10.1016/j.neuron.2013.04.014
46. Karch CM, Jeng AT, Nowotny P, Cady J, Cruchaga C, Goate AM. Expression of Novel Alzheimer's Disease Risk Genes in Control and Alzheimer's Disease Brains. Ginsberg SD, ed. *PLoS ONE*. 2012;7(11):e50976. doi:10.1371/journal.pone.0050976
47. Jiang T, Yu JT, Hu N, Tan MS, Zhu XC, Tan L. CD33 in Alzheimer's Disease. *Molecular Neurobiology*. 2013;49(1):529-535. doi:10.1007/s12035-013-8536-1
48. Bradshaw EM, Chibnik LB, Keenan BT, et al. CD33 Alzheimer's disease locus: altered monocyte function and amyloid biology. *Nature Neuroscience*. 2013;16(7):848-850. doi:10.1038/nn.3435
49. Gonzalez Y, Herrera MT, Soldevila G, et al. High glucose concentrations induce TNF-α production through the down-regulation of CD33 in primary human monocytes. *BMC Immunology*. 2012;13(1):19. doi:10.1186/1471-2172-13-19

50. Takahashi K, Prinz M, Stagi M, Chechneva O, Neumann H. TREM2-Transduced Myeloid Precursors Mediate Nervous Tissue Debris Clearance and Facilitate Recovery in an Animal Model of Multiple Sclerosis. Graeber M, ed. *PLoS Medicine*. 2007;4(4):e124. doi:10.1371/journal.pmed.0040124
51. Turnbull IR, Gilfillan S, Cella M, et al. Cutting Edge: TREM-2 Attenuates Macrophage Activation. *The Journal of Immunology*. 2006;177(6):3520-3524. doi:10.4049/jimmunol.177.6.3520
52. Zheng H, Liu CC, Atagi Y, et al. Opposing roles of the triggering receptor expressed on myeloid cells 2 and triggering receptor expressed on myeloid cells-like transcript 2 in microglia activation. *Neurobiology of Aging*. 2016;42:132-141. doi:10.1016/j.neurobiolaging.2016.03.004
53. Celarain N, Sánchez-Ruiz de Gordoa J, Zelaya MV, et al. TREM2 upregulation correlates with 5-hydroxymethycytosine enrichment in Alzheimer's disease hippocampus. *Clinical Epigenetics*. 2016;8:37. doi:10.1186/s13148-016-0202-9
54. Matarin M, Salih Dervis A, Yasvoina M, et al. A Genome-wide Gene-Expression Analysis and Database in Transgenic Mice during Development of Amyloid or Tau Pathology. *Cell Reports*. 2015;10(4):633-644. doi:10.1016/j.celrep.2014.12.041
55. Forabosco P, Ramasamy A, Trabzuni D, et al. Insights into TREM2 biology by network analysis of human brain gene expression data. *Neurobiology of Aging*. 2013;34(12):2699-2714. doi:10.1016/j.neurobiolaging.2013.05.001
56. Zhao Y, Wu X, Li X, et al. TREM2 Is a Receptor for β-Amyloid that Mediates Microglial Function. *Neuron*. 2018;97(5):1023-1031.e7. doi:10.1016/j.neuron.2018.01.031
57. N'Diaye EN, Branda CS, Branda SS, et al. TREM-2 (triggering receptor expressed on myeloid cells 2) is a phagocytic receptor for bacteria. *Journal of Cell Biology*. 2009;184(2):215-223. doi:10.1083/jcb.200808080
58. Hsieh CL, Koike M, Spusta SC, et al. A role for TREM2 ligands in the phagocytosis of apoptotic neuronal cells by microglia. *Journal of Neurochemistry*. 2009;109(4):1144-1156. doi:10.1111/j.1471-4159.2009.06042.x
59. Kawabori M, Kacimi R, Kauppinen T, et al. Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) Deficiency Attenuates Phagocytic Activities of Microglia and Exacerbates Ischemic Damage in Experimental Stroke. *Journal of Neuroscience*. 2015;35(8):3384-3396. doi:10.1523/jneurosci.2620-14.2015
60. Kobayashi M, Konishi H, Sayo A, Takai T, Kiyama H. TREM2/DAP12 Signal Elicits Proinflammatory Response in Microglia and Exacerbates Neuropathic Pain. *Journal of Neuroscience*. 2016;36(43):11138-11150. doi:10.1523/jneurosci.1238-16.2016
61. Bouchon A, Hernández-Munain C, Cella M, Colonna M. A DAP12-mediated pathway regulates expression of C Cchemokine receptor 7 and maturation of human dendritic cells. *The Journal of Experimental Medicine*. 2001;194(8):1111-1122. doi:10.1084/jem.194.8.1111
62. Guerreiro R, Wojtas A, Bras J, et al. TREM2 Variants in Alzheimer's Disease. *New England Journal of Medicine*. 2013;368(2):117-127. doi:10.1056/nejmoa1211851
63. Jonsson T, Stefansson H, Steinberg S, et al. Variant of TREM2 associated with the risk of Alzheimer's disease. *The New England journal of medicine*. 2013;368(2):107-116. doi:10.1056/NEJMoa1211103
64. Sims R, van der Lee SJ, Naj AC, et al. Rare coding variants in PLCG2, ABI3, and TREM2 implicate microglial-mediated innate immunity in Alzheimer's disease. *Nature Genetics*. 2017;49(9):1373-1384. doi:10.1038/ng.3916
65. Wang P, Guo Q, Zhou Y, et al. Lack of association between triggering receptor expressed on myeloid cells 2 polymorphism rs75932628 and late-onset Alzheimer's disease in a Chinese Han population. *Psychiatric Genetics*. 2018;28(1):16-18. doi:10.1097/ypg.0000000000000188