American Journal of Medicine and Medical Sciences 2023, 13(8): 1107-1113
DOI: 10.5923/j.ajmms.20231308.16

Role of Adhesion Molecules and Inflammatory Biomarkers in Ischemic Stroke

Abdurakhmonova K. B., Rakhimbaeva G. S.*

Department of Neurology, Tashkent Medical Academy, Tashkent, Uzbekistan

Abstract This article is devoted to a review of the literature, which presents on the role of adhesion molecules and inflammatory biomarkers in ischemic stroke, as well as aspects requiring detailed study on this issue.

Keywords Ischemic stroke, Inflammatory biomarkers, Adhesion molecules

1. Introduction

The World Health Organization defined “stroke” as a clinical syndrome characterized by a rapid onset of focal (or global in the case of coma) cerebral deficit lasting more than 24 h or leading to death, due to a vascular ischemic cause [1]. Ischemic stroke (IS) accounts for the majority of strokes and includes cryptogenic, lacunar, and thromboembolic strokes and it usually occurs when the blood supply to an area of the brain is interrupted [2]. Classical risk factors include age, cigarette smoking, diabetes, hypertension, and obesity. Prone-to-embolism diseases, such as cardiac valve disease and atrial fibrillation, increase the risk for IS, with the latter representing the most frequent condition. In IS, inflammation plays a pivotal role exerting both beneficial and detrimental effects. In fact, activation of resident cells, such as microglia, astrocytes, and endothelial cells is neuroprotective and promotes brain regeneration and recovery, whilst the recruitment of immune cells expressing inflammatory mediators and leading to blood-brain barrier (BBB) disruption is responsible for neuronal death, brain edema, and hemorrhagic transformation [3]. The sudden blockage of blood flow to the brain causes tissue hypoxia and triggers an inflammatory cascade leading to impairment of ion homeostasis, neuronal excitotoxicity, intracellular calcium overload, free radical generation, and lipid peroxidation ultimately determining neuronal injury [4].

2. Cellular Response to Ischemic Stroke

Inflammation is characterized by the accumulation of inflammatory cells and mediators in the ischemic brain. After ischemia onset, inflammatory cells such as blood-derived leukocytes and microglia are activated and accumulate within the brain tissue subsequently leading to inflammatory injury.

2.1. Leukocytes

4–6 h hours after ischemia onset, circulating leukocytes adhere to vessel walls, leading to migration and accumulation into ischemic brain tissue with subsequent release of proinflammatory mediators. These mediators lead to secondary injury of potentially salvageable tissue within the penumbra surrounding the infarct core. Neutrophils are generally the first leukocyte subtype recruited to the ischemic brain, and may potentiate injury by directly secreting deleterious substances or other inflammatory mediators [5]. In transient ischemia, several studies have shown that infarct volume is significantly reduced when neutrophil infiltration is inhibited [6,7,8,9]. Some mediators, while not directly cytotoxic, may be involved in the destruction of necrotic and neighboring viable tissue. Evidence that neutrophils potentiate ischemic injury includes numerous studies documenting improved neurological outcome following neutrophil depletion and inhibition of adhesion molecules which facilitate neutrophil entry into injured brain [10,11]. Lymphocytes are generally intended to play a negative role in ischemic brain pathogenesis even though there is also conflicting data. Following permanent middle cerebral artery occlusion (MCAO) in rats, lymphocytes were elevated in the ischemic lesion after neutrophils [12,13]. Preventing lymphocyte trafficking into ischemic brain ameliorated injury, suggesting that like neutrophils, lymphocytes also play a deleterious role [14]. Clinical studies also show that lymphocytes have a strong pro-inflammatory and tissue-damaging properties, and the upregulation of circulating lymphocytes are correlated to an increased risk of stroke recurrence and death [15]. However, in a study of cultured primary neurons, isolated neutrophils, but not lymphocytes potentiated neuronal injury due to excitotoxin exposure [16].

* Corresponding author:
rakhimbaeva.gs@mail.ru (Rakhimbaeva G. S.)
Received: Jul. 27, 2023; Accepted: Aug. 21, 2023; Published: Aug. 23, 2023
Published online at http://journal.sapub.org/ajmms

2.2. Microglial Cells and Circulating Monocytes / Macrophages

Soon after IS onset, microglia is activated and enhances circulating monocyte recruitment by releasing pro-inflammatory mediators, such as tumor necrosis factor (TNF)-α, nitric oxide (NO), and superoxide [17]. Among different possible microglia-activating stimuli, released adenosine triphosphate from damaged cells seems to play an important role in animal models [18]. Microglia activation exerts both beneficial and detrimental effects on stroke outcomes. Once activated, in fact, resident macrophages can polarize toward different phenotypes in response to local ischemic *milieu* ranging from classically activated, pro-inflammatory macrophages type 1 (M1) to alternatively activated macrophages type 2 (M2), which are mainly involved in the resolution of inflammation and tissue healing [19].

In contrast to early microglial response, monocyte-derived macrophages from bloodstream reach the damaged site most abundantly 3–7 days after ischemia onset during the chronic phase of IS [20]. Early after brain injury, an increased number of total monocytes in the blood circulation has been described in humans [21,22].

2.3. Astrocytes

Aside from traditional inflammatory cells, astrocytes are known to express different kinds of inflammatory mediators [23,24]. Following ischemia, brain astrocytes are activated resulting in increased glial fibrillary acidic protein (GFAP) expression and a so-called "reactive gliosis," characterized by specific structural and functional changes [25]. Like microglia, astrocyte proliferation follows two routes A1 a A2 reactive astrocytes. A1 reactive astrocytosis leads to the release of inflammatory factors, namely IL-6, tumor necrosis factor alfa (TNF-alfa), IL-1alfa, IL-1B and interferon gamma (IFNy) and free radicals. Post-stroke, due to failure of the Na+K + pump, astrocytes swell, leading to increased intracranial pressure and cerebral hypoperfusion [26,27]. A2 reactive astrocytes upregulate neurotrophic factors, playing an important role in neuroprotection [26,28]. Disconnection of the astrocyte endfeet and endothelial cells is involved in BBB damage and the influx of peripheral inflammatory cells [26]. In animal models, ischemic cerebral insult induce extensive astroglial response in the lesions core from 4 h to 1 day, peaking at day 4 and persisting until 28 days after [26].

2.4. Natural Killer (NK) Cells

Immune reactions are involved in all phases of ischemic cascade, and play an essential role in the determination of outcome after a brain ischemia [27,28]. Natural killer (NK) cells are important part of the innate immunity, and are among the first immune cells that make a response to a pathogen via cytolytic activity without prior sensitization. NK cells also regulate the adaptive immunity through cytokine production, and take control of antigen-specific immunologic memory [29]. Due to its immunological features that modulate innate and adaptive immune responses, NK cells receive greater emphasis in the study of ischemic stroke [30]. NK cells are among the first lymphocytes that occupy the brain parenchyma within hours after stroke onset, accompanied by T and B cells [31]. Kinetics study has shown that infiltration of NK cells begins within hours, reaches a peak at 3 days, and continues at least for 30 days after ischemia in the brain of a mouse [32]. The peak of NK cell infiltration is also noticed in 2 to 5 days post-mortem ischemic human brains [32]. It has been demonstrated that NK cells increase BBB disruption, catalyze neuronal death, and aggravate brain infarction following brain ischemia [33]. Moreover, reduction of NK cells in mice robustly decreases the brain infarction [32]. These brain-infiltrated NK cells have upregulated activating receptor NKG2D, and can directly kill neurons that have lost NK cell tolerance via loss of MHC Ib [33]. They are the main sources of interferon-gamma (IFN-γ), which can increase local inflammation, encourage glutamate release, and be the cause of hyperactivity and excitotoxicity in neurons [33]. NK cells also stimulate BBB disruption after brain ischemia through CXCL10-induced chemotaxis [32].

3. Inflammatory Mediators

3.1. Cytokines

Cytokines are small proteins that through extracellular signaling regulate different biological functions such as innate and acquired immunity, inflammation, proliferation and repair. Cytokines have both pro- and anti-inflammatory properties and play an important role in the progression of the stroke-associated inflammation [34,35,36].

3.1.1. Interleukin-1

IL-1 is a pro-inflammatory cytokine, which exists in two forms, IL-1α and IL-1β. Both forms signal through the IL-1 receptor type I, which can be competitively blocked by the receptor antagonist (IL-1Ra) [37]. Both IL-1α and IL-1β levels are elevated in the first hours following an IS. IL-1α is mainly secreted by microglia, while IL-1β is released by different compartments of the NVU [38]. It is surprising to note that IL-1 is not directly toxic, but it is able to activate astrocytes and endothelium favoring astrogliosis, release of chemokines, activation of metalloproteinase (MMP)-9, and release of vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1 [39,40].

3.1.2. Interleukin-4

IL-4 is a cytokine produced mainly by leukocytes. Its signaling contributes to a potent anti-inflammatory response through the inhibition of proinflammatory cytokines and chemokine among other functions [41]. Although it is poorly studied as a stroke biomarker, Kim and colleagues found that acute ischemic stroke patients had higher levels of IL-4 in serum than controls, [42] while similar IL-4 levels were

found in ischemic stroke patients with or without neurological worsening In reference to animal models, functional and cognitive improvement was shown following continuous (starting 6 h after ischemia and lasting for one week) IL-4 administration in a tMCAO mouse model, but without differences in infarct volume when compared with the control group. In contrast, others have found that IL-4 administration decreased infarct volume and improved the behavioral performance and neurological recovery 14 days after stroke in a tMCAO mouse model [43,44].

3.1.3. Interleukin-6

IL-6 is largely thought of as a pro-inflammatory cytokine, but whether it plays a significant role in ischemic stroke is far from clear. IL-6 deficient mice have similar sized infarcts compared to wildtype suggesting that it does not participate in ischemic pathogenesis [45]. However, other studies suggest either a beneficial or detrimental role. Clinical studies in stroke patients showed that serum concentrations of IL-6 had the strongest independent predictive value for in-hospital mortality [46]. In a double blind clinical trial on patients with acute stroke, IL-6 concentration was much lower in rhIL-1ra, a neuroprotective drug, treated patients, who showed a better outcome compared to placebo treated group [47].

3.1.4. Interleukin-10

IL-10, an anti-inflammatory cytokine, acts by inhibiting IL-1 and TNF-α and also by suppressing cytokine receptor expression and receptor activation. It is synthesized in the central nervous system (CNS) and is upregulated in experimental stroke [48]. Both exogenous administration [49]. and gene transfer of IL-10 [50] in cerebral ischemia models appear to have beneficial effects. Patients with acute ischemic stroke have an elevated numbers of peripheral blood mononuclear cells secreting IL-10 [51] and elevated concentrations in cerebrospinal fluid [52]. Furthermore, subjects with low IL-10 levels have an increased risk of stroke [53].

3.1.5. TNF-α

TNF-α is also upregulated in the brain after ischemia with similar expression patterns as IL-1beta. Initial increases are seen 1–3 h after ischemia onset [54], and, like IL-1beta, has a biphasic pattern of expression with a second peak at 24–36 h [55]. TNF-α expression was initially observed in neurons [56], then later in microglia and some astrocytes [57] as well as in the peripheral immune system [58]. TNF-α appears to have pleiotropic functions in the ischemic brain [59]. Inhibition of TNF-α reduces ischemic brain injury [60], while administration of recombinant TNF-α protein after stroke onset worsens ischemic brain damage [61]. However, TNF-α may also protect the brain under certain circumstances. TNF-α appears to be involved in the phenomenon of ischemic tolerance [62], and mice deficient in TNF receptors have larger infarcts [63]. The reasons for this disparity might be different pathways through which TNF-α signals.

3.2. Acute Phase Biomarkers

3.2.1. C-Reactive Protein (CRP)

CRP is a protein synthesized in the liver in response to IL-6 secretion by macrophages and T-cells [64]. High sensitivity CRP (Hs-CRP) is more sensitive and can more accurately detect low-grade inflammation. It correlates with cardiovascular risk in the general population and is an inflammatory biomarker frequently associated with all stages of IS [65,66]. CRP has been shown to be associated with an increased risk of all-cause mortality in patients with acute IS, predicts further ischemic events in patients with transient ischemic attack, lacunar stroke or IS in general [65,66]. Nevertheless, an increase of CRP occurs in IS but also in several other inflammatory conditions, reflecting its poor specificity and sensitivity [67] CRP is probably more informative with respect to acute indolent inflammatory status that very acute changes in stroke.

3.2.2. Procalcitonin (PCT)

PCT is a prohormone of calcitonin and is produced by C-cells and the thyroid gland [68]. Overall, there have been fewer studies than those on other biomarkers like CRP, reflecting its less frequent use in current practice. In ICH, serum PCT correlate with outcome, with higher PCR levels at admission being independently associated with unfavorable clinical outcome [69]. Another study combined albumin and PCT to uncover a ratio, where albumin/PCT ratio could be an additional diagnostic predictor for nosocomial infection in patients with ICH [70]. The role of PCT in CVT has not been investigated.

4. Cell Adhesion Molecules

Cell adhesion molecules (CAMs) play a key role in the trafficking and recruitment of leukocytes to activated endothelia in acute ischemic stroke. In fact, after the ischemic event, there is an increase in CAM expression on the cerebral endothelium. During the progression of inflammation, soluble isoforms of CAMs are shed from the cell surface and released into the bloodstream.

4.1. Intracellular Cell Adhesion Molecule – 1 (ICAM-1)

One of the best-known molecules involved in leukocyte adhesion is ICAM-1. After ischemia, proinflammatory cytokines such as TNF-α, IL-1 and interferon (IFN)-γ up-regulate ICAM-1 on both cerebral endothelial cells and neurons, which appears to be an important feature in driving leukocyte infiltration from blood to brain parenchyma [71]. Soluble ICAM-1 is increased in the blood and cerebrospinal fluid of acute ischemic stroke patients and is associated with neurological deterioration and early death after stroke [72]. On the other hand, the absence of differences in soluble

ICAM-1 levels between ischemic strokes and healthy controls has also been documented [73]. This paradox, however, can be partially explained by differences in the methodology used to detect ICAM-1 and the influence that some medications can have over the expression of adhesion molecules, such as non-steroid anti-inflammatory drugs [74]. Therefore, the use of circulating ICAM-1 levels as a biomarker of stroke diagnosis and inflammatory progression after ischemic stroke is not fully corroborated. Further research needs to be conducted to determine the ability of plasma ICAM-1 levels to discriminate ischemic stroke from other neurological and inflammatory diseases. Beyond its role as a biomarker, the inhibition of ICAM-1 has been shown to be neuroprotective by reducing neuronal damage in ischemic rats [75]. Studies of ICAM-1 knock-out mice also reported an improvement in blood flow and a reduction in infarct volume after an ischemic challenge [76], suggesting the impairment of leukocyte migration as a possible therapeutic strategy in improving stroke outcome. Furthermore, at the clinical level the Enlimomab Acute Stroke Trial (EAST) tested the efficacy and safety of inhibiting ICAM-1 through the administration of a murine anti-ICAM-1 antibody. Unfortunately, the Enlimomab-treated group of patients reported a significantly higher fatality rate than the placebo group [77], demonstrating the inefficacy of this therapeutic drug in stroke patients. Nevertheless, there is still some controversy in regards to the experimental design of EAST. The choice of the anti-ICAM-1 treatment regimen and the decision to perform a consecutive 5-day administration are suggested not to be optimally extrapolated parameters compared with the settings used in their respective studies performed in animal models of ischemia. For this reason, ICAM-1 is still suggested to be a possible therapeutic target for improving ischemic stroke outcome, as further studies might corroborate its benefits.

4.2. Vascular Cell Adhesion Molecule 1 (VCAM-1)

Vascular cell adhesion molecule 1 (VCAM-1) is also involved in stroke pathophysiology. VCAM-1, also known as CD106, is a cell surface protein expressed in the endothelium that mediates cell-cell recognition and leukocyte adhesion. VCAM-1 also participates in the downstream signal transduction originated after endothelium activation, directing the immune response to ischemia. High levels of soluble VCAM-1 have been detected in circulation after stroke [78]. Many other inflammatory diseases such as cardiopathies and cancer also present increased levels of soluble VCAM-1 in plasma, suggesting VCAM-1 as an indicator of an inflammatory state [79]. The upregulation of VCAM-1 after stroke is well documented in neurons and endothelial cells after ischemia, which is presumably caused by the elevated levels of cytokines after the ischemic event [72]. Ligand binding to VCAM-1 induces several metabolic and structural changes in endothelial cells that facilitate migration of leukocytes into the brain, which include the production of ROS and the subsequent activation of several MMPs [80]. Recently, VCAM-1 has also been found to participate in neuronal apoptosis after intracerebral hemorrhage, due to the pronounced increase of this adhesion molecule around the hematoma [81]. Thus, all these data attest to the involvement of VCAM-1 in the pathological processes following stroke. The major ligand of VCAM-1 is very late antigen-4 (VLA-4). VLA-4 is an integrin that is constitutively expressed in leukocyte plasma membranes. Upon leukocyte activation, VLA-4 undergoes conformational changes to bind VCAM-1, which contributes to leukocyte penetration of the brain tissue. Thus, VCAM-1/VLA-4 interaction has particular relevance in the immune response and leukocyte infiltration into areas of inflammation. Circulating VLA-4 levels have not been reported in stroke patients up to now, although further studies should check whether these proteins can be found in circulation (soluble form) and be used as inflammatory biomarkers.

5. Conclusions

IS remains a serious health risk in modern society. Despite the fact that great clinical progress has been made in recent years in order to improve diagnosis and treatment, beneficial long-term interventions, especially with regard to recovery, are still not available. We now know that the abrupt, dramatic inflammatory response immediately following IS can be evaluated as central or peripheral based on the brain or peripheral tissue origin. In recent years, our knowledge about macrophages has grown considerably as we now can consider M1 and M2 macrophage responses in the post-ischemic period. Apart from widely known cytokines, chemokines, DAMPs, and autoantibodies as well as CAMs represent important inflammatory mediators in the ischemic milieu and need to be considered in a prognostic perspective. Further trials are suggested in order to obtain more information on CAMs profile in order to appropriately select therapy according to each patient.

REFERENCES

[1] Warlow, C.; Sudlow, C.; Dennis, M.; Wardlaw, J.; Sandercock, P. Stroke. Lancet 2003, 362, 1211–1224.

[2] Writing Group Members; Lloyd-Jones, D.; Adams, R.J.; Brown, T.M.; Carnethon, M.; Dai, S.; de Simone, G.; Ferguson, T.B.; Ford, E.; Furie, K.; et al. Heart disease and stroke statistics—2010 Update: A report from the american heart association. Circulation 2010, 121, e46–e215.

[3] Jin, R.; Yang, G.; Li, G. Inflammatory mechanisms in ischemic stroke: Role of inflammatory cells. J. Leukoc. Biol. 2010, 87, 779–789.

[4] Petrovic-Djergovic, D.; Goonewardena, S.N.; Pinsky, D.J. Inflammatory disequilibrium in stroke. Circ. Res.2016, 119, 142–158.

[5] Hallenbeck JM. Significance of the inflammatory response in

brain ischemia. Acta Neurochir Suppl 1996; 66: 27–31.

[6] Bowes MP, Rothlein R, Fagan SC, Zivin JA. Monoclonal antibodies preventing leukocyte activation reduce experimental neurologic injury and enhance efficacy of thrombolytic therapy. Neurology 1995; 45: 815–819.

[7] Chopp M, Li Y, Jiang N, Zhang RL, Prostak J. Antibodies against adhesion molecules reduce apoptosis after transient middle cerebral artery occlusion in rat brain. J Cereb Blood Flow Metab 1996; 16: 578– 584.

[8] Clark WM, Lauten JD, Lessov N, Woodward W, Coull BM. The influence of antiadhesion therapies on leukocyte subset accumulation in central nervous system ischemia in rats. J Mol Neurosci 1995; 6: 43– 50.

[9] Yenari MA, Kunis D, Sun GH, Onley D, Watson L, Turner S, Whitaker S, Steinberg GK. Hu23F2G, an antibody recognizing the leukocyte CD11/CD18 integrin, reduces injury in a rabbit model of transient focal cerebral ischemia. Exp Neurol 1998; 153: 223–233.

[10] Hartl R, Schurer L, Schmid-Schonbein GW, del Zoppo GJ. Experimental antileukocyte interventions in cerebral ischemia. J Cereb Blood Flow Metab 1996; 16: 1108–1119.

[11] Zheng Z, Yenari MA. Post-ischemic inflammation: molecular mechanisms and therapeutic implications. Neurol Res 2004; 26: 884–892.

[12] Li GZ, Zhong D, Yang LM, Sun B, Zhong ZH, Yin YH, Cheng J, Yan BB, Li HL. Expression of interleukin-17 in ischemic brain tissue. Scand J Immunol 2005; 62: 481–486.

[13] Stevens SL, Bao J, Hollis J, Lessov NS, Clark WM, Stenzel-Poore MP. The use of flow cytometry to evaluate temporal changes in inflammatory cells following focal cerebral ischemia in mice. Brain Res 2002; 932: 110–119.

[14] Becker K, Kindrick D, Relton J, Harlan J, Winn R. Antibody to the alpha4 integrin decreases infarct size in transient focal cerebral ischemia in rats. Stroke 2001; 32: 206–211.

[15] Nadareishvili ZG, Li H, Wright V, Maric D, Warach S, Hallenbeck JM, Dambrosia J, Barker JL, Baird AE. Elevated pro-inflammatory CD4+CD28- lymphocytes and stroke recurrence and death. Neurology 2004; 63: 1446–1451.

[16] Dinkel K, Dhabhar FS, Sapolsky RM. Neurotoxic effects of polymorphonuclear granulocytes on hippocampal primary cultures. Proc Natl Acad Sci U S A 2004; 101: 331–336.

[17] Jin, R.; Yang, G.; Li, G. Inflammatory mechanisms in ischemic stroke: Role of inflammatory cells. J. Leukoc. Biol. 2010, 87, 779–789.

[18] Davalos, D.; Grutzendler, J.; Yang, G.; Kim, J.V.; Zuo, Y.; Jung, S.; Littman, D.R.; Dustin, M.L.; Gan, W.B. ATP mediates rapid microglial response to local brain injury in vivo. Nat. Neurosci. 2005, 8, 752–758.

[19] Prinz, M.; Priller, J. Microglia and brain macrophages in the molecular age: From origin to neuropsychiatric disease. Nat. Rev. Neurosci. 2014, 15, 300–312.

[20] Breckwoldt, M.O.; Chen, J.W.; Stangenberg, L.; Aikawa, E.; Rodriguez, E.; Qiu, S.; Moskowitz, M.A.; Weissleder, R. Tracking the inflammatory response in stroke in vivo by sensing the enzyme myeloperoxidase. Proc. Natl. Acad. Sci. USA 2008, 105, 18584–18589.

[21] Kaito, M.; Araya, S.; Gondo, Y.; Fujita, M.; Minato, N.; Nakanishi, M.; Matsui, M. Relevance of distinct monocyte subsets to clinical course of ischemic stroke patients. PLoS ONE 2013, 8, e69409.

[22] Perego, C.; Fumagalli, S.; de Simoni, M.G. Temporal pattern of expression and colocalization of microglia/macrophage phenotype markers following brain ischemic injury in mice. J. Neuroinflamm. 2011, 8, 174.

[23] Benveniste EN. Cytokine actions in the central nervous system. Cytokine Growth Factor Rev 1998; 9: 259– 275, 1998.

[24] Che X, Ye W, Panga L, Wu DC, Yang GY. Monocyte chemoattractant protein-1 expressed in neurons and astrocytes during focal ischemia in mice. Brain Res 2001; 902: 171–177.

[25] Pekny M, Nilsson M. Astrocyte activation and reactive gliosis. Glia 2005; 50: 427–434.

[26] Jayaraj, R.L.; Azimullah, S.; Beiram, R.; Jalal, F.Y.; Rosenberg, G.A. Neuroinflammation: Friend and foe for ischemic stroke. J. Neuroinflamm. 2019, 16, 142.

[27] Iadecola C, Anrather J: The immunology of stroke: from mechanisms to translation. Nat Med 2011; 17: 796-808.

[28] Macrez R, Ali C, Toutirais O, Le Mauff B, Defer G, Dirnagl U, Vivien D: Stroke and the immune system: from pathophysiology to new therapeutic strategies. Lancet Neurol 2011; 10: 471-480.

[29] Cerwenka A, Lanier LL: Natural killer cell memory in infection, inflammation and cancer. Nat Rev Immunol 2016; 16: 112-123.

[30] Vivier E, Raulet DH, Moretta A, Caligiuri MA, Zitvogel L, Lanier LL, Yokoyama WM, Ugolini S: Innate or adaptive immunity? The example of natural killer cells. Science 2011; 331: 44-49.

[31] Gelderblom M, Leypoldt F, Steinbach K, Behrens D, Choe CU, Siler DA, Arumugam TV, Orthey E, Gerloff C, Tolosa E, Magnus T: Temporal and spatial dynamics of cerebral immune cell accumulation in stroke. Stroke 2009; 40: 1849-1857.

[32] Zhang Y, Gao Z, Wang D, Zhang T, Sun B, Mu L, Wang J, Liu Y, Kong Q, Liu X, Zhang Y, Zhang H, He J, Li H, Wang G: Accumulation of natural killer cells in ischemic brain tissues and the chemotactic effect of IP-10. J Neuroinflammation 2014; 11: 79.

[33] Gan Y, Liu Q, Wu W, Yin JX, Bai XF, Shen R, Wang Y, Chen J, La Cava A, Poursine-Laurent J, Yokoyama W, Shi FD: Ischemic neurons recruit natural killer cells that accelerate brain infarction. Proc Natl Acad Sci U S A 2014; 111: 2704-2709.

[34] Xu, S.; Lu, J.; Shao, A.; Zhang, J.H.; Zhang, J. Glial Cells: Role of the Immune Response in Ischemic Stroke. Front. Immunol. 2020, 11, 294.

[35] Jiang, C.; Wu, W.; Deng, Y.; Ge, J. Modulators of microglia activation and polarization in ischemic stroke (Review). Mol. Med. Rep. 2020, 21, 2006–2018.

[36] Zhang JM and An J. Cytokines, inflammation, and pain. Int Anesthesiol Clin 2007; 45: 27–37.

[37] Murray, K.N.; Parry-Jones, A.R.; Allan, S.M. Interleukin-1 and acute brain injury. Front. Cell. Neurosci. 2015, 9, 18.

[38] Luheshi, N.M.; Kovacs, K.J.; Lopez-Castejon, G.; Brough, D.; Denes, A. Interleukin-1α expression precedes IL-1β after ischemic brain injury and is localised to areas of focal neuronal loss and penumbral tissues. J. Neuroinflamm. 2011, 8, 186.

[39] Herx, L.M.; Yong, V.W. Interleukin-1β is required for the early evolution of reactive astrogliosis following CNS lesion. J. Neuropathol. Exp. Neurol. 2001, 60, 961–971.

[40] Thornton, P.; Pinteaux, E.; Allan, S.M.; Rothwell, N.J. Matrix metalloproteinase-9 and urokinase plasminogen activator mediate interleukin-1-induced neurotoxicity. Mol. Cell. Neurosci. 2008, 37, 135–142.

[41] Allen, C.; Thornton, P.; Denes, A.; McColl, B.W.; Pierozynski, A.; Monestier, M.; Pinteaux, E.; Rothwell, N.J.; Allan, S.M. Neutrophil cerebrovascular transmigration triggers rapid neurotoxicity through release of proteases associated with decondensed DNA. J. Immunol. 2012, 189, 381–392.

[42] Gadani SP, Cronk JC, Norris GT, et al. Interleukin-4: a cytokine to remember. J Immunol 2013; 189: 4213–4219

[43] Kim HM, Shin HY, Jeong HJ, et al. Reduced IL-2 but elevated IL-4, IL-6, and IgE serum levels in patients with cerebral infarction during the acute stage. J Mol Neurosci 2000; 14: 191–196.

[44] Zhao X, Wang H, Sun G, et al. Neuronal interleukin-4 as a modulator of microglial pathways and ischemic brain damage. J Neurosci 2015; 35: 11281–11291.

[45] Clark WM, Rinker LG, Lessov NS, Hazel K, Hill JK, Stenzel-Poore M, Eckenstein F. Lack of interleukin-6 expression is not protective against focal central nervous system ischemia. Stroke 2000; 31: 1715–1720.

[46] Herrmann O, Tarabin V, Suzuki S, Attigah N, Coserea I, Schneider A, Vogel J, Prinz S, Schwab S, Monyer H, Brombacher F, Schwaninger M. Regulation of body temperature and neuroprotection by endogenous interleukin-6 in cerebral ischemia. J Cereb Blood Flow Metab 2003; 23: 406–415.

[47] Rallidis LS, Vikelis M, Panagiotakos DB, Rizos I, Zolindaki MG, Kaliva K, Kremastinos DT. Inflammatory markers and in-hospital mortality in acute ischaemic stroke. Atherosclerosis. 2005.

[48] Emsley HC, Smith CJ, Georgiou RF, Vail A, Hopkins SJ, Rothwell NJ, Tyrrell PJ. A randomised phase II study of interleukin-1 receptor antagonist in acute stroke patients. J Neurol Neurosurg Psychiatry 2005; 76: 1366–1372.

[49] Strle K, Zhou JH, Shen WH, Broussard SR, Johnson RW, Freund GG, Dantzer R, Kelley KW. Interleukin-10 in the brain. Crit Rev Immunol 2001; 21: 427–449.

[50] Spera PA, Ellison JA, Feuerstein GZ, Barone FC. IL-10 reduces rat brain injury following focal stroke. Neurosci Lett 1998; 251: 189–192.

[51] Ooboshi H, Ibayashi S, Shichita T, Kumai Y, Takada J, Ago T, Arakawa S, Sugimori H, Kamouchi M, Kitazono T, Iida M. Postischemic gene transfer of interleukin-10 protects against both focal and global brain ischemia. Circulation 2005; 111: 913–919.

[52] Pelidou SH, Kostulas N, Matusevicius D, Kivisakk P, Kostulas V, Link H. High levels of IL-10 secreting cells are present in blood in cerebrovascular diseases. Eur J Neurol 1999; 6: 437–442.

[53] Tarkowski E, Rosengren L, Blomstrand C, Wikkelso C, Jensen C, Ekholm S, Tarkowski A. Intrathecal release of pro- and anti-inflammatory cytokines during stroke. Clin Exp Immunol 1997; 110: 492– 499.

[54] 54. van Exel E, Gussekloo J, de Craen AJ, Bootsma-van der Wiel A, Frolich M, Westendorp RG. Inflammation and stroke: the Leiden 85-Plus Study. Stroke 2002; 33: 1135–1138.

[55] Liu T, Clark RK, McDonnell PC, Young PR, White RF, Barone FC, Feuerstein GZ. Tumor necrosis factor-alpha expression in ischemic neurons. Stroke 1994; 25: 1481–1488.

[56] Murakami Y, Saito K, Hara A, Zhu Y, Sudo K, Niwa M, Fujii H, Wada H, Ishiguro H, Mori H, Seishima M. Increases in tumor necrosis factor-alpha following transient global cerebral ischemia do not contribute to neuron death in mouse hippocampus. J Neurochem 2005; 93: 1616–1622.

[57] Uno H, Matsuyama T, Akita H, Nishimura H, Sugita M. Induction of tumor necrosis factor-alpha in the mouse hippocampus following transient forebrain ischemia. J Cereb Blood Flow Metab 1997; 17: 491–499.

[58] Offner H, Subramanian S, Parker SM, Afentoulis ME, Vandenbark AA, Hurn PD. Experimental stroke induces massive, rapid activation of the peripheral immune system. J Cereb Blood Flow Metab 2006;26:654–665

[59] Hallenbeck JM. The many faces of tumor necrosis factor in stroke. Nat Med 2002; 8.

[60] Yang GY, Gong C, Qin Z, Ye W, Mao Y, Bertz AL. Inhibition of TNF alpha attenuates infarct volume and ICAM-1 expression in ischemic mouse brain. Neuroreport 1998; 9: 2131–2134.

[61] Barone FC, Arvin B, White RF, Miller A, Webb CL, Willette RN, Lysko PG, Feuerstein GZ. Tumor necrosis factor-alpha. A mediator of focal ischemic brain injury. Stroke 1997; 28: 1233–1244.

[62] Ginis I, Jaiswal R, Klimanis D, Liu J, Greenspon J, Hallenbeck JM. TNF-alpha-induced tolerance to ischemic injury involves differential control of NF-kappaB transactivation: the role of NF-kappaB association with p300 adaptor. J Cereb Blood Flow Metab 2002; 22: 142–152.

[63] Bruce AJ, Boling W, Kindy MS, Peschon J, Kraemer PJ, Carpenter MK, Holtsberg FW, Mattson MP. Altered neuronal and microglial responses to excitotoxic and ischemic brain injury in mice lacking TNF receptors. Nat Med 1996; 2: 788–794.

[64] Thompson, D.; Pepys, M.B.; Wood, S.P. The physiological structure of human C-reactive protein and its complex with phosphocholine. Structure 1999, 7, 169–177.

[65] Mengozzi, M.; Kirkham, F.A.; Girdwood, E.E.R.; Bunting, E.; Drazich, E.; Timeyin, J.; Ghezzi, P.; Rajkumar, C. C-Reactive Protein Predicts Further Ischemic Events in Patients with Transient Ischemic Attack or Lacunar Stroke. Front. Immunol.

2020, 11, 1403.

[66] Yu, B.; Yang, P.; Xu, X.; Shao, L. C-reactive protein for predicting all-cause mortality in patients with acute ischemic stroke: A meta-analysis. Biosci. Rep. 2019, 39.

[67] Bonaventura, A.; Liberale, L.; Vecchié, A.; Casula, M.; Carbone, F.; Dallegri, F.; Montecucco, F. Update on Inflammatory Biomarkers and Treatments in Ischemic Stroke. Int. J. Mol. Sci. 2016, 17, 1967.

[68] Tian, D.; Zhang, S.; He, X.; Liu, H. Serum procalcitonin as a diagnostic marker in acute ischemic stroke. NeuroReport 2015, 26, 33–37.

[69] He, D.; Zhang, Y.; Zhang, B.; Jian, W.; Deng, X.; Yang, Y.; Xiao, T.; Yu, H.; Wen, S.; Huang, K. Serum Procalcitonin Levels are Associated with Clinical Outcome in Intracerebral Hemorrhage. Cell. Mol. Neurobiol. 2017, 38, 727–733.

[70] Deng, S.; Gao, J.; Zhao, Z.; Tian, M.; Li, Y.; Gong, Y. Albumin/Procalcitonin Ratio Is a Sensitive Early Marker of Nosocomial Blood Stream Infection in Patients with Intra-Cerebral Hemorrhage. Surg. Infect. 2019, 20, 643–649.

[71] L. Jing, J. Wang, J. Zhang, C. Cao, Y. Chang, J. Dong, F. Guo, P.A. Li, Upregulation of ICAM-1 in diabetic rats after transient forebrain ischemia and reperfusion injury, J. Inflamm. 11 (35) (2014) 1–11.

[72] C.J.M. Frijns, L.J. Kappelle, Inflammatory cell adhesion molecules in ischemic cerebrovascular disease, Stroke 33 (8) (Aug. 2002) 2115–2122.

[73] V. Supanc, Z. Biloglav, V.B. Kes, V. Demarin, Role of cell adhesionmolecules in acute ischemic stroke, Ann. Saudi Med. 31 (4) (2011) 365–370.

[74] C.J.M. Frijns, L.J. Kappelle, Inflammatory cell adhesion molecules in ischemic cerebrovascular disease, Stroke 33 (8) (Aug. 2002) 2115–2122.

[75] J. Cao, X. Shi, W. Li, J. Liu, X. Miao, J. Xu, Protective effect of anti-intercellular adhesion molecule-1 antibody on global cerebral ischemia/reperfusion injury in the rat, Biosci. Trends 3 (2) (2009) 48–52.

[76] E.S. Connolly, C.J. Winfree, T.A. Springer, Y. Naka, H. Liao, S.D. Yan, D.M. Stern, R.A. Solomon, D.J. Pinsky, Cerebral protection in homozygous null ICAM-1 mice after middle cerebral artery occlusion role of neutrophil adhesion in the pathogenesis of stroke, J. Clin. Invest. 97 (1) (1996) 209–216.

[77] EAST, Use of anti-ICAM-1 therapy in ischemic stroke results of the Enlimomab Acute Stroke Trial, Neurology 57 (2001) 1428–1434.

[78] R. Brondani, C.R.M. Rieder, D. Valente, L.F. Araújo, N. Clausell, Levels of vascular cell adhesion molecule-1 and endothelin-1 in ischemic stroke: a longitudinal prospective study, Clin. Biochem. 40 (2007) 282–284.

[79] A. Papayianni, E. Alexopoulos, P. Giamalis, L. Gionanlis, A. Belechri, P. Koukoudis, D.Memmos, Circulating levels of ICAM-1, VCAM-1, and MCP-1 are increased in haemodialysis patients: association with inflammation, dyslipidaemia, and vascular events, Nephrol. Dial. Transplant. 17 (2002) 435–441.

[80] T.L. Deem, J.M. Cook-mills, Vascular cell adhesion molecule 1 (VCAM-1) activation of endothelial cell matrix metalloproteinases: role of reactive oxygen species, Blood 104 (8) (2009) 2385–2393.

[81] D. Zhang, D. Yuan, J. Shen, Y. Yan, C. Gong, J. Gu, H. Xue, Y. Qian,W. Zhang, X. He, L. Yao, Y. Ji, A. Shen, Up-regulation of VCAM1 relates to neuronal apoptosis after intracerebral hemorrhage in adult rats, Neurochem. Res. (Apr. 2015).