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REVIEW ARTICLE

The Role of Inflammatory Response in Stroke Associated Programmed Cell Death

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Abstract: Stroke represents devastating pathology which is associated with a high morbidity and mortality. Initial damage caused directly by the onset of stroke, primary injury, may be eclipsed by secondary injury which may have a much more devastating effect on the brain. Primary injury is predominantly associated with necrotic cell death due to fatal insufficiency of oxygen and glucose. Secondary injury may on the contrary, lead apoptotic cell death due to structural damage which is not compatible with cellular functions or which may even represent the danger of malign transformation. The immune system is responsible for surveillance, defense and healing processes and the immune system plays a major role in triggering programmed cell death. Severe pathologies, such as stroke, are often associated with deregulation of the immune system, resulting in aggravation of secondary brain injury. The goal of this article is to overview the current knowledge about the role of immune system in the pathophysiology of stroke with respect to programmed neuronal cell death as well as to discuss current therapeutic strategies targeting inflammation after stroke.

Keywords: Inflammation, stroke, necrosis, apoptosis, necroptosis, pyroptosis, autophagy.

1. INTRODUCTION

Stroke is a sudden neurological dysfunction caused by an interruption of blood supply to the brain. Stroke is a major source of long term disability and mortality, it is the number two cause of death worldwide [1]. Each year, approximately 15 million people worldwide suffer from a stroke, from which around one third die and another one third stay permanently disabled [2]. Interruption of blood supply to the brain may be caused by cerebral vessel occlusion causing ischemic stroke (around 70% of strokes) or by vessel rupture leading to hemorrhagic stroke (around 30% of strokes) [3]. Rupture of intraparenchymal artery results in intracerebral hemorrhage (ICH), while the rupture of an extraparenchymal cerebral artery (localized in subarachnoid space) results in subarachnoid hemorrhage (SAH). A cerebral aneurysm is the most common source of spontaneous (non-traumatic) subarachnoid hemorrhage (SAH). Although the hemorrhagic stroke is less frequent than ischemic, hemorrhagic stroke is associated with a higher mortality and altogether it accounts for around same number of deaths as ischemic stroke [3]. Pathological changes similar to stroke may occur also in "a small scale" as a part of small vessel disease which may have a very complex pathophysiological background [4]. In this article, we will outline main pathophysiological processes associated with stroke with an accent to the inflammation and cell death after stroke. Stroke research is a very dynamic process, new information about pathophysiology of stroke allow researchers to view the problematic from new perspectives and to create new models for research which in turn may bring new information [5, 6].

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2. PATHOPHYSIOLOGY OF STROKE

As mentioned above, stroke is a sudden loss of neural functions due to interruption of blood supply to the brain due to ischemic or hemorrhagic event. Neurons are highly metabolically active and almost completely dependent on oxidative phosphorylation [7]. The neurons use the majority of energy to keep the membrane electrical activity and neuronal cells are very sensitive to restriction of oxygen and glucose [8]. Blood supply interruption causes quick development of brain damage which may be reversible or irreversible according to severity of stroke.

Primary brain injury is a direct damage which develops immediately after the onset of stroke due to critical ischemia or due to tissue disruption by hematoma. Critical ischemia results in irreversible neuronal damage forming the core of infarction. In the core of infarction absolute insufficiency of ATP leads to depolarization and bioenergetic failure, the ATP dependent ion pumps are not able to keep minimal required membrane potential, osmotically active ions, such as

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Na^+, accumulates inside the cell, followed by water influx which result in cytotoxic edema and potentially cell death [7]. Disruption of brain tissue by hematoma is a direct mechanical damage caused by mass effect of extravasated blood [9].

Secondary injury develops in a delayed manner and the main contributors to secondary injury are excitotoxicity, oxidative stress and inflammation [7, 10, 11]. The most severe consequences of secondary brain injury are endothelial damage (and subsequent vasogenic edema) or neuronal cell death [7, 10, 11]. In ischemic stroke, the secondary damage occurs mainly in the penumbra, the area surrounding the core of infarction, where the neuronal cells are affected by ischemia reversibly [12]. Insufficiency of ATP due to decreased blood supply leads to neuronal depolarization, but there is enough ATP to avoid complete bioenergetic failure as occurs in ischemic core. In experimental conditions, ATP levels in the penumbra decreased to 62% of basal production, while in the core of infarction ATP levels reached 22% of basal production [13]. Delayed ischemic cerebral damage, similar to penumbral, has been described after both types of hemorrhagic stroke, although there are still some controversies about this topic in the pathophysiology of ICH [14-16]. Mass effect associated with large intracerebral hemorrhage cause ischemia in perihematomal area due to increased intracerebral pressure [9, 17]. However, increased intracerebral pressure may not be associated with cerebral ischemia in all the cases and this was described in experimental conditions [16]. Increased intracerebral pressure in patients with ICH together with decreased blood pressure and preexisting cerebral microangiopathy due to atherosclerosis was thus hypothesized to be major pathophysiological factors for ischemic cerebral damage after ICH [14]. If there are some controversies about cerebral ischemia after ICH, there seems to be no controversies in case of SAH. It is generally accepted that the mass effect of blood in subarachnoid space after SAH cause a massive increase in intracranial pressure, resulting in transient cerebral ischemia, which play an important role in the pathophysiology of SAH [11, 18].

Massive extracellular accumulation of excitatory neurotransmitters, excitotoxicity, is due to increased release from depolarized neurons and due to decreased reuptake which is ATP dependent. Excitotoxicity amplifies depolarization of surrounding neurons, leading to influx and accumulation of Na^+, Cl^- and Ca^{2+} [19]. Ionic imbalance and especially high intracellular level of Ca^{2+} may result in excessive activation of proteolytic and reactive oxygen species (ROS) producing enzymes and potentiate secondary neuronal damage [7,19].

Excessive production of reactive oxygen species, oxidative stress, is a significant contributor to secondary injury in stroke [20]. Stroke associated oxidative stress is a very complex process involving several pathophysiological processes including excessive accumulation of Ca^{2+} in the cytoplasm, mitochondrial dysfunction, decreased activity of anti-oxidant enzymes and inflammation [21-23]. Neurons are vulnerable to oxidative stress because of high metabolic activity, relatively low amount of antioxidant enzymes and high levels of polyunsaturated fatty acids which are prone to oxidative damage [24]. High level of oxidative stress occurs mainly during reperfusion [21]. Reperfusion injury is a severe complication following restoration of blood supply and in most severe cases, hemorrhagic transformation of the ischemic area may occur [7].

Following intracerebral hemorrhage, or hemorrhagic transformation, several cytotoxic blood components are in contact with brain parenchyma, which may contribute to secondary injury. These include complement molecules, coagulation factors, immunoglobulin molecules and mainly iron from depredated hemoglobin [10, 25]. Subarachnoid hematoma is localized extraparenchymally and the blood is in contact with main stems of cerebral vessels. The cytotoxic blood components may contribute to cerebral vasospasm development, however, other etiological factors, including NO, endothelial cell damage or oxidative stress may be involved in cerebral vasospasm development [26-28]. Cerebral vasospasm represents the most severe late complication after SAH, which is associated with high mortality and morbidity [29]. Unclear pathophysiology of cerebral vasospasm and the absence of effective treatment led to the identification and further research of early brain injury, pathological processes which precede and which may contribute to cerebral vasospasm development [11, 30, 31]. Although these pathological processes basically represent secondary injury, the term "early brain injury" is more appropriate from the perspective of cerebral vasospasm development.

3. THE ACUTE INFLAMMATORY RESPONSE IN STROKE

Inflammation plays a crucial role in the pathophysiology of stroke; on one side the inflammatory response is necessary for tissue repair, on the other side the inflammatory response is an important contributor to secondary brain injury after stroke [32, 33]. The inflammatory response is quite uniform in ischemic and hemorrhagic stroke, including activation of microglia and endothelial cells in the first step, followed by infiltration of affected areas by peripheral leukocytes which subsequently cause tissue damage (Fig. **1**) [34-36]. Although the basic concept of inflammatory response after stroke is generally known, there is still a lot of missing information and this concept is constantly updated [37].

Microglia represents resident immune cells in central nervous system responsible for immunological surveillance and phagocytic functions [38]. Microglial activation occurs rapidly after stroke in reaction to ischemia/tissue damage [39-41]. Microglial activation may also be induced by endothelial cells, suggesting the important role of microvasculature after stroke [42]. Activated microglia is morphologically and functionally similar to macrophages [43]. The role of activated microglia is ambiguous. Activated microglia may have neuroprotective role, possibly by its phagocytic functions [39]. But activated microglia is mainly a source of neurotoxic substances, including proteases, excitatory amino acids, nitric oxide and pro-inflammatory cytokines [44, 45].

Endothelial cell activation includes increased expression of selectins and adhesion molecules, which is an essential step for recruitment of leukocytes from peripheral blood [46]. Both E-selectin and P-selectin are involved in leuko-

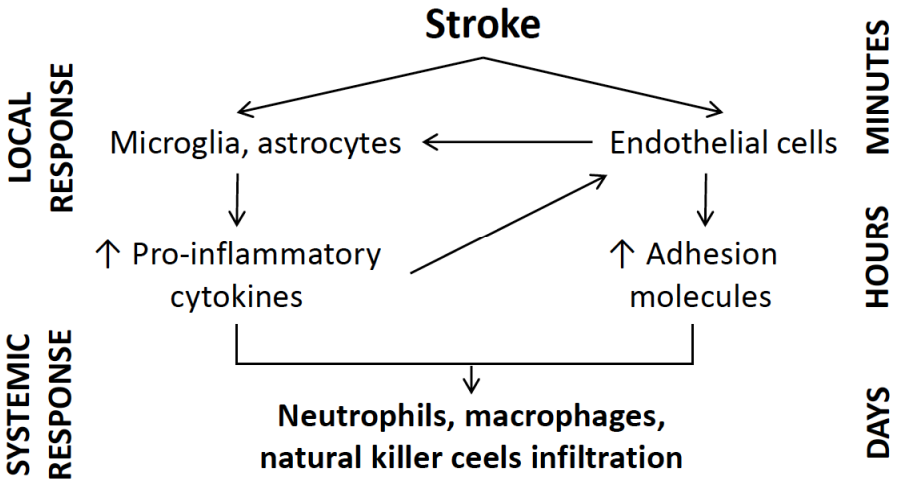

Fig. (1). The inflammatory response after stroke and its spatial and temporal context. Stroke associated tissue ischemia/damage is strong pro-inflammatory signal, which activates resident immune cells (microglia) as well as astrocytes and endothelial cells, resulting in the production of pro-inflammatory cytokines and adhesion molecules. Pro-inflammatory cytokines help to activate endothelial cells locally, but they are mainly released into circulation, where they activate peripheral leukocytes (mainly neutrophils, macrophages and natural killers). Activated leukocytes from the periphery are directed by the adhesion molecules, which allow the leukocytes to infiltrate the affected areas.

cyte rolling and recruitment and are associated with secondary brain injury, while the L-eslectin seems not to be related to stroke [47-49]. Adhesion molecules facilitate diapedesis of leukocytes through the vessel wall and while there are strong evidences that ICAM-1 contribute to secondary brain injury, reports about the role of VCAM-1 in the pathophysiology of stroke are controversial [50-55].

Peripheral leukocytes infiltrate the affected area in response to microglial and endothelial activation. The kinetics of leukocytes after ischemic as well as hemorrhagic stroke is as follows: the first infiltrating cells are neutrophils, followed by macrophages and natural killer cells with subsequent infiltration of T lymphocytes [56]. The deleterious effect of escalated inflammatory response is mainly associated with toxic effect of ROS species, arachidonic acid metabolites and pro-inflammatory cytokines which significantly contribute to secondary brain damage [57]. It is still not clear whether the inflammatory response associated with severe stroke may be considered as a deregulated or just exaggerated, but regulated process. Regulatory T lymphocytes play crucial role in maintaining immune homeostasis and controlling inflammation and these cells are recently a subject intensive research [58].

4. INFLAMMATION AND CELL DEATH AFTER STROKE

Inflammation plays crucial role in the pathophysiology of stroke and inflammation is closely associated with cell death [57]. On one side, tissue damage induces an inflammatory response in order to remove debris and repair tissue damage, on the other side, strong/deregulated inflammatory response may aggravate the tissue damage and cell death [57]. As mentioned above, harmful effect of inflammation is associated with a toxic effect of ROS species, proteolytic enzymes and pro-inflammatory cytokines. The immune cells are rich source of these mediators and while the ROS as well as proteolytic enzymes may cause direct tissue damage, the effect of pro-inflammatory cytokines is receptor mediated process (Fig. **2**) [57]. Several subtypes of cell death have been described and these are characterized by a different level of regulation, but all subtypes are closely interconnected and associated with inflammation [59]. Apoptosis and necrosis may be considered as two opposite poles of cell death scale. Necrosis is unregulated or minimally regulated, passive process which does not require too much energy, while apoptosis is highly regulated, active process requiring energy [60,61]. Necrosis induces inflammation, while apoptosis does not induce inflammation, on contrary apoptosis may be induced by inflammation [59]. Necrosis occurs under "pathological" conditions, while apoptosis occurs either under "physiological" conditions during development or under "pathological" conditions as a result of intrinsic "self-eliminating" mechanisms or immune surveillance [59]. Necroptosis, pyroptosis and autophagy are the other subtypes of cell death, which will be described below, however, all the subtypes of cell death are closely interconnected, possibly as the backup programs and immune system may coordinate interactions between them [62, 63].

4.1. Necrosis

Although this article is primarily focused on programmed cell death, it is important to consider all forms of cell death and that is why this part was included in this review. Necrosis is a type of cell death, which is minimally regulated or unregulated at all [60, 61]. It usually occurs in the core of infarction or in areas damaged directly by the mass effect of hematoma, so this type of cell death is typically associated with primary injury [7, 9]. Due to extreme conditions, bioenergetic failure may occur with subsequent cytotoxic edema and cellular lysis [7]. Bioenergetic failure is a passive, not regulated, process, which develops quickly and we may assume that no regulation occurs because there is not time and energy for it. In less severe conditions, necrosis may occur as

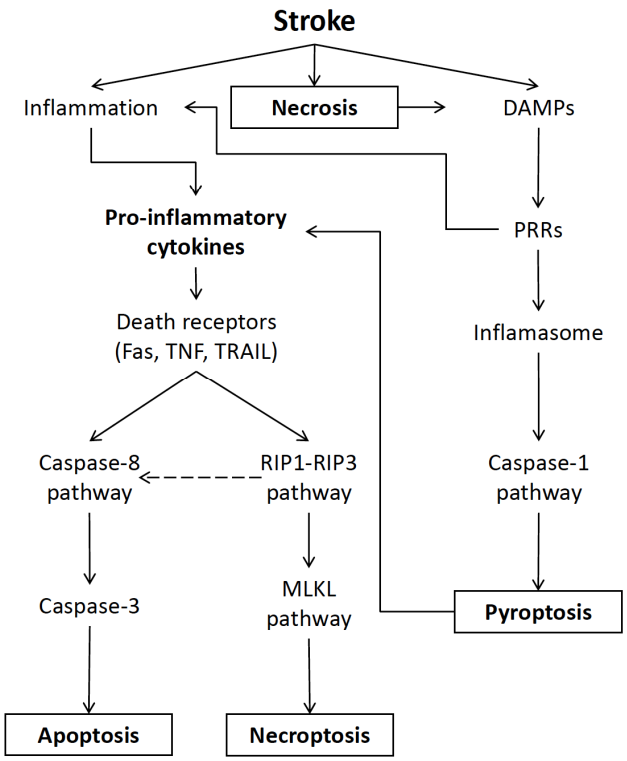

Fig. (2). The inflammatory response and cell death after stroke. DAMPs (damage associated molecular pattern) are released from injured/necrotic cells in response to tissue damage. Inflammation is triggered in response to DAMPs through PRRs (pattern recognition receptors). Pro-inflammatory cytokines act through death receptors (Fas, TNF, TRAIL) triggering either caspase-8 apoptotic pathway (extrinsic), or RIP1-RIP3 (receptor-interacting protein kinases)-MLKL (mixed-lineage kinase domain-like protein) pathway resulting in necroptosis. The RIP1-RIP3 pathway may induce apoptosis when MLKL is not present. PRRs also contribute to inflammation by induction of inflamasome formation and caspase-1 activation, resulting in maturation and releasing of pro-inflammatory cytokines from the pyroptotic cells.

partially regulated process initiated by oxidative stress, high Ca^{2+}cytoplasmatic concentrations and mediated by calpain mechanism [64-67]. Necrotic cell death is associated with an activation of immune system [39, 40].

4.2. Apoptosis

Apoptosis is a highly regulated type of cell death, which develops in a delayed manner and which is associated with secondary injury. Apoptosis typically occurs in ischemic penumbra and apoptosis also plays an important role in the pathophysiology of hemorrhagic stroke [7, 68, 69]. Cellular component degradation in apoptosomes and cell shrinkage are characteristics of this type of cell death. Apoptosis is mediated by caspase pathways, which may be triggered by intrinsic or extrinsic factors. The intrinsic pathway is induced by cellular/mitochondrial damage, leading to cytochrome c release from mitochondria, which activates caspase 9 - caspase 3 [70]. The extrinsic pathway is mediated by surface death receptors, from which the most important are Fas, TNF and TRAIL receptors associated with activation of Caspase 8 and Caspase 10 [71]. This may lead to activation of intrinsic pathway or to direct activation of executioner caspase 3 [72]. Caspase 3 is the final step of activation for both intrinsic and extrinsic pathways mediating programmed cell death, mainly by enhancing DNA damage and fragmentation [73]. The immune system plays crucial role in apoptosis regulation and excessive inflammatory response is associated with induction of pro-apoptotic and inhibition of anti-apoptotic pathways [74].

4.3. Necroptosis

Necroptosis is a programmed type of cell death combining features of apoptosis (initial phase) and necrosis (executive phase). Necroptosis is mediated by same receptors as apoptosis, different signaling pathways are, however, associated with these two subtypes of cell death. Fas, TNF and TRAIL activation is, in case of necroptosis, caspase independent machinery associated with RIP1-RIP3 (receptor-interacting protein kinases) signaling pathway [75]. RIP1-RIP3 complex activates MLKL (mixed-lineage kinase domain-like protein) which induce necroptotic cell death by permeabilization of plasmatic membrane [76-78]. MLKL is essential for necroptosis execution, because an activation of RIP3 in absence of MLKL induces caspase dependent machinery, which result in apoptosis, suggesting that the selection of "executive program" (necroptosis or apoptosis) possibly depends on the levels of signaling and effector proteins [79]. Necroptosis was suggested as a potential back up plan for the situations when the caspase mediated cell death program fails [80]. Necroptosis was also reported to be associated with extremely pathological extracellular conditions, such as acidosis, which is associated with ASIC1 (acid-sensing ion channel 1) mediated activation of the RIP1-RIP3 system [77]. This may represent a potential shortcut in case

when the severe environmental conditions do not allow realizing apoptotic program.

4.4. Pyroptosis

Pyroptosis is a type of programmed cell death, which is associated with a high level of inflammatory response. The inflammatory response is triggered by PRRs (pattern recognition receptors) which recognize a wide range of microbial structures called PAMPs (pathogen associated molecular pattern), endogenous stress signals called DAMPs (damage associated molecular pattern) or ASC (apoptosis speck-like) proteins and induce formation of inflamasommes [81, 82]. Important compounds of inflammasomes are NLRPs (NOD-like receptors containing pyrin domains), mainly NLRP 1 and NLRP3 which interact with pro- caspase-1 and cleave it into active the form [81, 82]. Caspase 1 in turn cleaves precursors of inflammatory cytokines activating mainly IL-1β, IL-18 and IL-33 which are released from dying cells and induce inflammation [81, 82].

4.5. Autophagy

Autophagy is a basic cellular function enabling degradation of cellular content in autophagosomes [83]. This process is enhanced under stress conditions such as stroke and maybe both beneficial and deleterious [84, 85]. Cellular components degradation and recyclation may help to keep energy homeostasis and the physiological level of autophagy was demonstrated to be protective, while insufficient or excessive level of autophagy was shown to be harmful [86]. Three types of autophagy were described: macroautophagy, microautophagy and chaperone-mediated autophagy. Macroautophagy is the predominant pathway involved in recycling and degradation of cytoplasmic content in autophagosomes which fuse with lysosome, forming autolysosome [87]. Microautophagy is non-selective degradation of cytoplasmic substances in the lysosomes [88]. Finally chaperone-mediated autophagy represents selective degradation of cytoplasmic material bound to chaperone [89]. Autophagy plays a crucial role in degradation of cytoplasmic proteins, lipids, as well as whole organelles such as mitochondria, endoplasmatic reticulum or ribosomes [90-93]. Autophagy is tightly regulated, the major regulatory pathways are AMPK (AMP-activated protein kinase) pathway which is involved in positive modulation, and mTOR (mammalian target of rapamycine) pathway which represents negative modulator [94].

5. INFLAMMATION AS THERAPEUTIC TARGET AFTER STROKE

Inflammatory response after stroke may be considered as a two step process. The first step is an activation of the immune system and leukocyte trafficking, in the second step infiltrating leukocytes execute their functions with all the consequences. Therapeutic interventions basically target either leukocyte trafficking or crucial mediators of inflammatory response. However, it is necessary to mention that many important details regarding inflammatory response after stroke are still not known, and, for example, the serum levels of TNFα in patients with intracerebral hemorrhage have not been investigated in a robust clinical study [95].

ICAM-1 (intercellular adhesion molecule 1, CD54) is adhesion molecule which is necessary for neutrophil transendothelial migration [96]. In experimental conditions, the anti-ICAM-1 antibody reduced neutrophil infiltration into the brain and this was associated with reduced ischemic brain damage in transient focal cerebral ischemia model [97]. Phase III clinical trial with anti-ICAM-1 antibody enlimomab, however, failed to prove the protective effect of this treatment in acute stroke patients and treatment was even associated with higher infarct volume and mortality [98]. Further examination found that administration of anti-ICAM-1 antibody induced production of host antibodies against the medicament and activation of the immune system including neutrophils, complement and endothelial cells [99].

Blockade of IL-1 receptor using antagonist IL-1RA decreased cerebral ischemia injury in experimental conditions, but in phase II clinical trial IL-1RA did not improve infarct volume, survival or outcome of acute stroke patients [100, 101]. Peripheral administration of medication was suggested as a possible reason for clinical trial failure and intranasal administration was postulated as a potential solution [102].

Minocycline is a broad-spectrum tetracycline antibiotic with neuroprotective, anti-inflammatory and anti-oxidative properties [103, 104]. Minocycline down-regulate microglial activation, TNFα expression and T cell activation [105]. The neuroprotective effect of minocycline was reported in both ischemic and hemorrhagic stroke models [106-108]. Minocycline improved outcome of acute ischemic stroke patients in an open-label, evaluator-blinded study, but the phase IV clinical trial did not confirm the previous results and was terminated for futility [109, 110]. Phase I clinical trial testing the effectiveness of minocycline in patients with intracerebral hemorrhage is currently in progress [111].

Fingolimod is an agonist of sphingosine-1-phosphate receptor, which prevents lymphocytes to egress from lymphoid organs and decreases expression of ICAM-1 [112, 113]. Fingolimod was also reported to decrease activity of cytotoxic T-cells independently of S1P receptor [114]. The beneficial effect of fingolimod was described in both ischemic and hemorrhagic stroke in animal models [113, 115, 116]. In an open-label, evaluator blinded study in acute ischemic stroke patients, orally administered fingolimod decreased circulating lymphocytes, reduced infarct volume, attenuated neurological deficit and promoted recovery [117]. In a multi-center pilot trial, the combination therapy with fingolimod and alteplase reduced reperfusion injury and improved outcome in acute ischemic stroke patients [118]. The neuroprotecive effect of fingolimod was also reported in patients suffering from ICH. In a pilot two arms, evaluator blinded study, fingolimod reduced perihematomal edema, attenuated neurological deficit and promoted recovery in patients with a small supratentorial hematoma [119].

PPAR-γ (peroxisome proliferator-activated receptor gamma) agonists have multiple effects including attenuation of inflammatory response. PPAR-γ is a nuclear receptor responsible for transcription of several products participating in lipid and glucose metabolism, as well as in inflammatory response [120, 121]. PPAR-γ agonist rosiglitazon attenuated

experimentally induced ischemic brain injury by reducing pro-inflammatory cytokines and chemokines expression and this was associated with decreased neutrophil infiltration into the brain [122]. Rosiglitzaone also decreased neuronal damage and improved functional outcome in experimentally induced intracerebral hematoma and this was associated with the improved phagocytic function of microglia, which promotes hematoma resolution [123]. Phase II clinical trial testing safety of PPAR- γ agonist Pioglitazone for hematoma resolution after intracerebral hemorrhage has been completed [124].

Celecoxib is a selective inhibitor of cyclooxygenase 2 which was reported to reduce inflammation, brain edema and perihematomal cell death in experimentally induced ICH [125]. In a small multi-center study, celecoxib reduced perihematomal edema in patients with ICH [126].

Simvastatin is hypolipidemicum with additional effects including improving endothelial functions and decreasing vascular inflammation [127]. Simvastatin is considered to be an effective prophylaxis against cerebral vasospasm development after SAH and anti-vasospastic and anti-inflammatory properties are recently tested in phase III clinical trial [128, 129].

Etanercept is TNFα inhibitor, which is currently in phase I clinical trial in patients with aneurysmal subarachnoid hemorrhage [130].

CONCLUSION

Inflammation plays an important role in the pathophysiology of stroke and it is closely associated with cell death after stroke. Both the inflammation and cell death are very complex pathophysiological processes. Thanks to both experimental and clinical research, we have a lot of information, but we are still far from understanding these crucial processes in their complexity. And possibly that is why we are not able to effectively control either inflammation or cell death when exaggerated. More research is needed in this field in order to elucidate the interconnections between inflammation and different types of cell death in its complexity. It is very desirable, because it may allow us to develop a more complex therapeutic approach to patients suffering from stroke. Complex therapeutic approach targeting inflammatory response as well as employing new technologies in diagnostics and management may improve the effectiveness of treatment, reducing neuronal cell death after stroke and improving patients outcome after stroke [131, 132].

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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