Global brain inflammation in stroke

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Stroke, including acute ischaemic stroke and intracerebral haemorrhage, results in neuronal cell death and the release of factors such as damage-associated molecular patterns (DAMPs) that elicit localised inflammation in the injured brain region. Such focal brain inflammation aggravates secondary brain injury by exacerbating blood–brain barrier damage, microvascular failure, brain oedema, oxidative stress, and by directly inducing neuronal cell death. In addition to inflammation localised to the injured brain region, a growing body of evidence suggests that inflammatory responses after a stroke occur and persist throughout the entire brain. Global brain inflammation might continuously shape the evolving pathology after a stroke and affect the patients' long-term neurological outcome. Future efforts towards understanding the mechanisms governing the emergence of so-called global brain inflammation would facilitate modulation of this inflammation as a potential therapeutic strategy for stroke.

Introduction

Acute ischaemic stroke and intracerebral haemorrhage affect millions of people annually across the world. Most people surviving a stroke are not able to live independently and are at an increased risk of developing additional neurological sequelae, such as dementia.[1–4] The acute nature, severity, and unpredictability of stroke engender substantial physical and emotional consequences for patients and their families. Stroke produces immediate neurological deficits, and in severe cases the resultant mass effect and brain oedema can progress to brain herniation and death. The primary brain injury after ischaemia or haemorrhage is followed by secondary brain injury, which begins within minutes and persists for days to weeks or even longer.[5,6] Secondary brain injury is incited by a series of trigger events, including direct brain compression from mass effect, coagulation abnormalities, release and degradation of blood components, intracellular biochemical cascades, and inflammation.[7–9]

Over 20 years ago, Polly Matzinger proposed the so-called danger theory, which states that the immune system is activated via danger signals—cell death products—produced by the body's own cells.[10] Although the primary injury mechanisms differ between acute ischaemic stroke and intracerebral haemorrhage, the damage to neural cells and release of damage-associated molecular patterns (DAMPs) defines a common pathway that fuels the innate and adaptive immune response within the brain and perhaps, the periphery.[1,11] However, the nature of brain inflammation after a stroke, and especially its long-term consequences, is incompletely defined in the medical literature. Following an acute focal brain injury during stroke, neural cell death orchestrates a secondary immune response characterised by glial activation, recruitment of peripheral immune cells, and release of cytokines and chemokines.[1,12–15] These processes, initiated within minutes, are concentrated within the lesion and surrounding tissue and persist for weeks thereafter.[14] We characterise these processes as focal brain inflammation, which refers to a localised region of inflammation adjacent to the brain lesion. In addition to focal brain inflammation, emerging evidence from imaging of live patients, post-mortem studies, and animal experiments suggests that a distinct and less recognised state of brain inflammation, which we refer to as global brain inflammation, develops following stroke. Global brain inflammation features neuroinflammation, which occurs remote from the site of primary injury and exhibits a unique temporal evolution. The temporal and spatial evolution of global brain inflammation suggests its profound yet less well defined role in stroke pathophysiology.

In this Personal View, we describe the development of global brain inflammation in stroke according to existing evidence and contrast the salient features of global brain inflammation relative to focal brain inflammation to understand its provenance and the potential effects on clinical outcome. Finally, we discuss the role of future research in understanding the biological underpinnings of global brain inflammation to inform potential development of a rationalised immune intervention as a primary or adjunctive approach to treat stroke.

Primary and secondary brain injury after stroke

Primary brain injury occurs immediately after the onset of stroke and is often irreversible. In ischaemic stroke, the abrupt cessation of blood supply in a vascular territory results in the death of neural cells, engendering an ischaemic core, surrounded by a hypoperfused region termed the penumbra. In intracerebral haemorrhage, the rupture of a blood vessel leads to extravasation of blood components directly into the brain, forming a haematoma that provokes structural damage. Cells affected by this initial injury trigger a rapid cascade of events including, but not limited to, excitotoxicity, oxidative stress, and mitochondrial disturbance; all of which promote secondary brain injury.[1] Following brain haemorrhage, the activation of thrombin and release of clot components (eg, haemoglobin and iron) are also involved.[16] Evolutionary conservation of a self-protective response might be involved in limiting brain damage and promoting repair. However, such responses are often less well tuned in the setting of overwhelming injury during acute stroke. Substantial literature supports the multifactorial involvement of secondary events in the progression of neuronal

damage, blood–brain barrier disruption, and cerebral oedema.[1,5]

Initiation of inflammation following stroke

Stroke triggers a robust inflammatory response. Despite divergent pathogenic processes of primary injury, activation of immune response occurs similarly in both ischaemic and haemorrhagic stroke. The immune response is initiated by the release of DAMPs from injured cells.[17,18] A common spectrum of DAMPs, including adenosine, heat shock proteins, high mobility group box 1, and interleukin (IL)-33, are involved in both acute ischaemic stroke and intracerebral haemorrhage.[11,18] DAMPs are subsequently detected by immune cells bearing corresponding pattern recognition receptors, which mediate the activation of intracellular signalling pathways. Additionally, in intracerebral haemorrhage, blood components and coagulation factors that are released into the brain also function as danger signals that trigger immune responses.[19] Microglia in the CNS are among the very first cell populations to react to these danger signals. Within minutes following injury, microglia are activated, undergo morphological change, and secrete cytokines.[20] As the most abundant glial cells in the brain, astrocytes actively participate in the immune response after injury by recruiting peripheral immune cells[21] and interacting with microglia[22,33] via secreting cytokines and chemokines. Additionally, astrocytes might also support the survival of ischaemic neurons during the acute phase.[23] Activation of endothelial cells in the CNS,[7,24] platelet dysregulation,[25,26] and invasion of peripheral myeloid cells and lymphocytes[8,27,28] drive the progression of inflammation, contributing to the damage of brain parenchyma and vasculature.[9] Breakdown of the blood–brain barrier takes place early after a stroke[29] and facilitates the infiltration of peripheral leucocytes to the injured brain. Cyclically, leucocytes further aggravate the blood–brain barrier disruption by releasing proinflammatory cytokines, reactive oxygen species, and matrix metalloproteinases.[27,30]

During the acute stage of brain injury, the focal inflammation aggravates brain injury by enhancing excitotoxicity, direct cytolysis, oxidative stress, and thromboinflammation. These events in turn propagate microvascular dysfunction, oedema expansion, and ultimately worsens the clinical outcome.[5,8,9] Conversely, focal brain inflammation might also participate in debris clearance, neurotrophin production, and immune regulation, and these roles evolve distinctly over time.[31–33]

Evidence for global brain inflammation in stroke

Evidence derived from studies in humans (table) and animal models of stroke increasingly suggests that immune responses occur in areas remote from the injury site in both acute and chronic phases of stroke. Global brain inflammation features similar cellular and molecular components as focal brain inflammation, but global brain inflammation evolves in a distinct profile.

Glial activation

Global distribution of activated microglia in the chronic phase of stroke is a prominent feature of global brain inflammation after a stroke. Activated microglia gradually decrease at the injury site after several weeks but appear in distal brain regions and become globally distributed within several months. The temporal and spatial dynamics of microglial activation after a stroke in patients with acute ischaemic stroke has been characterised by a PET scan with a radioactive ligand of the translocator protein that is highly expressed by activated microglia (ie, PK11195-PET scan). With this approach, activated microglia have been shown to accumulate focally within a week of disease onset and can be detected in distal regions after several months.[34–36] A combination of PK11195-PET scan with diffusion tensor imaging MRI further shows the distribution of activated microglia along the pyramidal tract to the thalamus and pons,[37,38] which implies an association between anterograde degeneration and inflammation. In an observational study[39] that included 16 patients with middle cerebral artery territory infarcts, PK11195 binding increased in the non-infarct ipsilateral area during the subacute phase (13–28 days after a stroke), coincident with neuronal loss in this area as determined by flumazenil-PET at a late stage (6–21 weeks after a stroke). These findings provide direct evidence supporting the association of microglia activation and secondary neurodegeneration in the distal area. In the area of salvaged penumbra exhibiting significant neuronal loss, PK11195 binding was mild and not substantially increased, indicating a distinct inflammatory process between the focal lesion and distal brain regions.[39] Translocator protein is also expressed by monocytes or macrophages and to a lesser extent, by astrocytes, which reduce the specificity of PK11195 imaging.[43] Nevertheless, this approach offers an opportunity for in-vivo monitoring of neuroinflammation in patients. The aforementioned spatial and temporal evolution profile of microglia in patients was mirrored in rodent models of brain ischaemia induced by middle cerebral artery occlusion. Although focal microglial activation peaked at about 1 week after ischaemia and subsequently ablated over 1 month,[44–47] the distribution of activated microglia progressively developed in the midbrain, pons, and contralateral regions in subsequent months.[48,49] In an endothelin-1-induced prefrontal infarct rat model, activated microglia were detected in remote cortex and white matter at 28 days after ischaemia; this finding was associated with neuronal loss in these areas.[50]

Evidence for global brain inflammation in patients with intracerebral haemorrhage has just begun to emerge. An observational study[41] of both PK11195-PET and dynamic contrast enhanced MRI in five patients with intracerebral haemorrhage detected an accumulation of activated microglia and blood–brain barrier damage surrounding the haematoma in a timeframe of 7–25 days. Although healthy controls were not included in this study, the PK11195 signal nonetheless shows a trend towards a

	Patients included (n)	Control group (n)	Approaches	Disease phase during detection	Findings	Limitations
Acute ischaemic stroke						
Cross-sectional[34]	Ischemic stroke (6)	..	PK11195-PET	3–150 days after a stroke	Increased microglia activation can be detected as early as 3 days in the lesion area, and distributed to distal brain areas at later time points	Small sample size, heterogeneity in stroke patterns, and no controls
Cross-sectional[35]	Middle cerebral artery territory infarct (7)	..	PK11195-PET	2–24 months after a stroke	Increased microglia activation in ipsilateral thalamus, a degeneration area remote from the primary injury	Small sample size and no controls
Prospective longitudinal[36]	Middle cerebral artery territory infarct (4)	Healthy controls (4)	PK11195-PET	≤72 h; 7–14 days; 25–30 days after a stroke	Minimal microglia activation was seen before 72 h, beyond which time activation rises in the infarct core, peri-infarct region, and contralateral hemisphere up to 30 days	Small sample size
Prospective non-longitudinal[37]	First time acute subcortical ischaemia affecting the pyramidal tract (11)	First time acute subcortical ischaemia without involvement of the pyramidal tract (10)	PK11195-PET and DTI	Within 2 weeks of onset	Remote microglia activation was detected in the pyramidal tract that was affected by stroke	Small sample size and no healthy controls
Prospective longitudinal[38]	First-ever, subcortical stroke (18)	Transient ischemic attack (6)	PK11195-PET	2 weeks to 6 months after a stroke	Microglia are activated in the infarct initially and decrease significantly over follow-up; remote activated microglia were detected in the brain stem along the affected pyramidal tract, and persisted during follow-up	Small sample size and no healthy controls
Prospective longitudinal[39]	Middle cerebral artery stroke, with CT perfusion confirmed penumbra and early neurological improvement* (16)	Healthy controls for FMZ-PET (12), PK11195-PET (10)	FMZ-PET and PK11195-PET	PK11195-PET within 13–28 days; FMZ-PET within 6–21 weeks	Increased microglia activation in the area of secondary remote degeneration, but not in the penumbra area	Small sample size and long-term microglial activation was not detected
Prospective longitudinal[40]	Ischaemic stroke within 48 h of onset (54)	..	DCE-MRI	48 h to 5–7 days after a stroke	Blood–brain barrier permeability was increased even in vessel territories remote from the index infarct	Heterogeneity in stroke patterns, small sample size, and absence of long-term evaluation
Intracerebral haemorrhage						
Cross-sectional[41]	Acute ICH (5)	..	PK11195-PET and DCE-MRI	7 to 25 days after haemorrhage	Blood–brain barrier leakage and activated microglia were substantially increased in the perihaematomal region; activated microglia distributed globally to a lesser extent than in the perihaematomal region	Small sample size and no controls
Histopathological case-control[42]	Fatal ICH (30)	Patients who died of other non-cerebrovascular diseases (6)	Immunohistochemical staining	2 h to 5 days after a stroke	NF-κB p65, MIP-2, and MMP9 were upregulated on bilateral hippocampi and cerebellum	Absence of immune cells staining

PK11195 is a ^{11}C-labelled translocator protein ligand for PET imaging of brain inflammation. Translocator protein is highly expressed by activated microglia and is also expressed by peripheral monocytes and, to a lesser extent, astrocytes. ICH=intracerebral haemorrhage. DTI= diffusion tensor imaging. DCE=Dynamic contrast enhanced. FMZ=^{11}C-flumazenil, radioligand to visualise neurons. NF-κB=nuclear factor-kappa B. MIP-2=macrophage inflammatory protein-2. MMP9=matrix metalloproteinase-9. *Early neurological improvement is defined as gain in National Institute of Health Stroke Scale score of ≥8 within the first 24 h or a score ≤2 at 24 h.

Table: **Evidence of global brain inflammation in patients with stroke**

disseminated distribution. The results of this study also suggest that focal brain inflammation is sustained longer in intracerebral haemorrhage relative to acute ischaemic stroke, wherein focal brain inflammation subsides after about 1 week.[1,51]

Clinical evidence supporting a role for astrocytes in global brain inflammation after a stroke is still absent. One reason might be the absence of a specific astrocyte biomarker feasible for in-vivo imaging in patients who have had a stroke.[52] Future long-term (ie, over years) monitoring of glial activation by imaging or post-mortem pathological study would be crucial to answer whether the global glial activation is persistent after a stroke.

Mobilisation of peripheral immune cells after stroke

Because of an absence of direct accessibility and specific imaging approaches, the evidence for peripheral immune cell contribution to global brain inflammation in patients

is scarce. Nevertheless, animal studies suggest the involvement of these cells in global brain inflammation. In a murine model of middle cerebral artery occlusion, myeloid cells and lymphocytes were identified in the contralateral hemisphere throughout both acute and chronic phases, although the cell count was lower than that seen in focal brain inflammation.[53,54] These cells are found continuously in the ischaemic brain at least 2 weeks after a stroke.[54,55] Accumulation of T cells within the thalamus, which is distal to primary injury and known to develop secondary neurodegeneration after a stroke, has been observed.[54] Experimental studies[1,55] suggest that B cells have a small role in the formation of focal brain injury during the acute phase. However, the evidence of immunoglobulin synthesis in CSF of patients with stroke suggests that the humoral immune response is activated in stroke.[56] Additionally, experimental studies[56,57] found that B cells accumulate and deposit immunoglobulins in the hippocampus beyond the region of initial ischaemic injury, and that this process is associated with cognitive dysfunction of mice.[57] These data implicate the humoral immune components in the development of global brain inflammation. However, the experimental evidence of peripheral immune cells in intracerebral haemorrhage is absent.

Role for soluble inflammatory mediators

Inflammatory mediators, including cytokines and chemokines, can be produced by multiple cell types in the brain after stroke. In a murine model of acute ischaemic stroke, an array of cytokines including IL-1β, IL-6, tumour necrosis factor-α (TNF-α), and transforming growth factor β is observed in the contralateral hemisphere during the acute phase after ischaemia.[58] Another study[55] of mice showed that IL-1α, IL-1β, interferon-γ, TNF-α, and IL-6 concentrations are elevated 2 weeks after a stroke in whole brain tissue, and this increase was accompanied by infiltration of lymphocytes. A post-mortem histopathological case–control study of 30 brains of patients with intracerebral haemorrhage who died from 2 h to 5 days following the intracerebral haemorrhage onset identified upregulation of nuclear factor-κB p65 subunit, macrophage inflammatory protein-2, and matrix metalloproteinase 9 in the contralateral hippocampus and cerebellum, although to a lesser extent compared with the injured hemisphere.[42] This study suggests that global brain inflammation is initiated early after intracerebral haemorrhage. Similar results have been reported in rodent models of intracerebral haemorrhage, in which elevated mRNA levels of IL-1β, IL-6, transforming growth factor β, TNF-α, and IL-27 were found in the contralateral hemisphere from hours to 7 days after haemorrhage.[31,59]

Vascular inflammation

Endothelial cell activation and vascular inflammation are hallmarks of stroke. Cerebral microvascular endothelial cells are swiftly activated after a stroke and upregulate a series proinflammatory and procoagulation factors, including vascular cell adhesion molecule (VCAM-1) and matrix metalloproteinase 9. These molecules subsequently promote the adhesion and migration of peripheral leukocytes, activation of the coagulation system, and blood–brain barrier disruption.[7,9] Two studies[40,61] published in 2017 also show a global vascular response after a stroke. In acute ischaemic stroke, global blood–brain barrier leakage was shown by a dynamic contrast enhanced MRI study evaluating 54 patients during the acute phase of ischaemia.[40] Advances in molecular imaging techniques have allowed for specific visualisation of vascular inflammation in experimental animals.[24] For instance, MRI imaging with microparticles of iron oxide targeted to VCAM-1 has shown that VCAM-1 is globally upregulated in brain vessels of middle cerebral artery occlusion mice as early as 24 h after the procedure and persists for at least 5 days.[60] Moreover, in a transient ischaemic attack mouse model induced by 15 min occlusion of middle cerebral artery, p-selectin was upregulated globally 24 h after onset of an acute ischaemic attack.[61] Radiofluorinated matrix metalloproteinase inhibitor [^{18}F]BR-351 has been developed for PET imaging of matrix metalloproteinases. Although [^{18}F]BR-351 tracer uptake was increased in the infarct and peri-infarct region within 1 week of brain ischaemia, accumulation of the marker in the contralateral hemisphere increased at 3 weeks, during which the signal intensity became similar to that of the ipsilateral hemisphere,[44] suggesting global blood–brain barrier damage in the chronic phase of ischaemia. Similar to acute ischaemic stroke, molecular imaging of VCAM-1 in intracerebral haemorrhage models also suggest a wide distribution of vascular inflammation in the acute phase of intracerebral haemorrhage.[60] Similar global vascular inflammation was also detected in a mouse model of subarachnoid haemorrhage.[62]

Potential mechanisms governing the initiation and maintenance of global brain inflammation

Many aspects of the initiation and development of global brain inflammation after stroke are unclear. Nevertheless, some evidence implicates the potential mechanisms driving the development of global brain inflammation. Stroke induces an acute inflammatory response in the CSF, characterised by elevated concentrations of cytokines like IL-6 and leucocytes.[63–67] Therefore, a putative pathway mediating the initiation of global brain inflammation might be the spread of inflammatory components through CSF and extracellular space. Additionally, cytokines might also transmit inflammatory signals to remote areas via volume transmission.[68] Moreover, a chronic elevation of systemic inflammatory mediators such as C-reactive protein, IL-6, and TNF-α is reported in patients,[69] which is associated with decline of cognition[70] and stroke recurrence.[71,72] This evidence indicates that systemic inflammatory response might influence chronic brain inflammation.

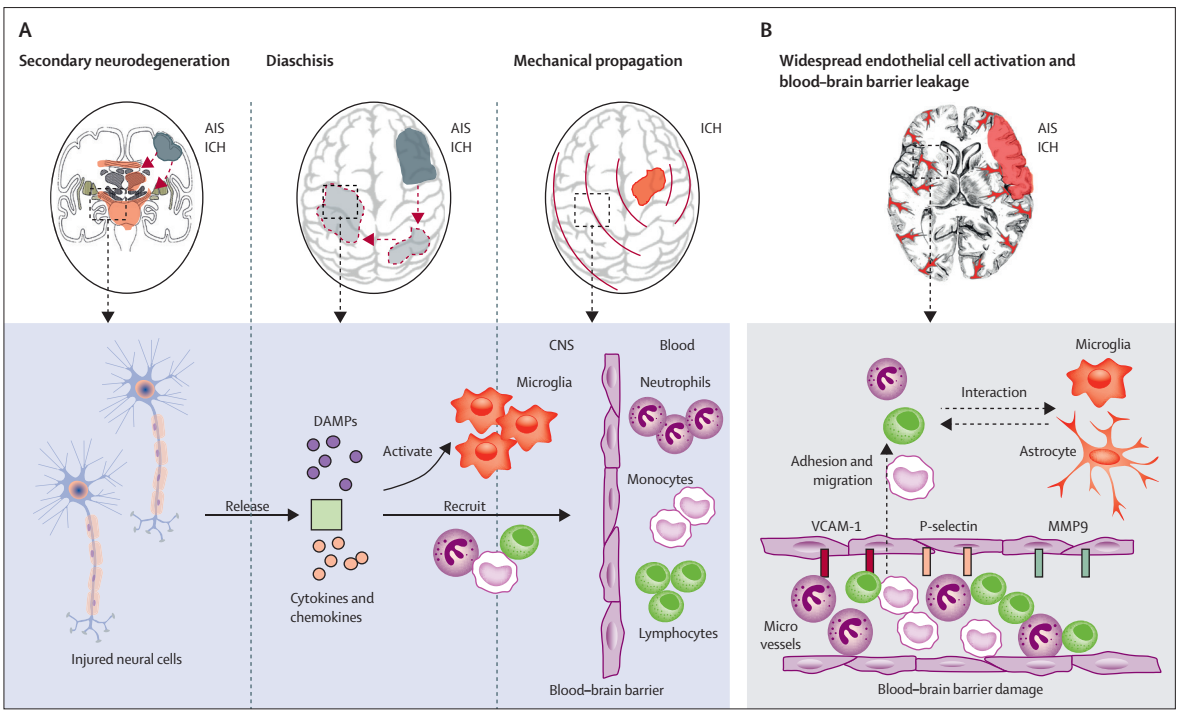

Figure: **Mechanisms governing the emergence of global brain inflammation in stroke**
(A) Brain injury associated with acute ischaemic stroke or intracerebral haemorrhage can induce secondary neurodegeneration and diaschisis, which can further cause remote white matter damage or neuronal loss. Additionally, in ICH, intracranial propagation of mechanical force stemming from haematoma leads to distal diffuse brain injury. The damaged neurons or white matter then release DAMPs or cytokines and chemokines. These molecules can subsequently activate microglia and astrocytes, and recruit peripheral immune cells including myeloid cells and lymphocytes, thereby triggering the initiation of inflammation in the remote area. (B) Acute stroke can induce widespread endothelial cell activation, characterised by upregulation of a battery of molecules including VCAM-1, P-selectin, matrix metalloproteinases, and increased leakage of the blood–brain barrier, which globally facilitate adhesion and migration of peripheral leukocytes to the brain parenchyma and damage of microvasculature. These peripheral immune cells subsequently interact with glial cells and boost remote brain inflammation. AIS=acute ischaemic stroke. DAMP=damage-associated molecular pattern. ICH=intracerebral haemorrhage. MMP9=matrix metallopeptidase 9. VCAM-1=vascular adhesion molecule 1.

Retrograde and anterograde degeneration after a stroke can promote extended whiter matter injury and remote neuronal loss. Glial cells including microglia and astrocytes are known to react to myelin damage.[73] Therefore, glial cells might be sequentially activated by remote white matter damage, as supported by PET imaging studies, which show that remote neuroinflammation is mainly localised to the structures or areas that developed neurodegeneration.[37–39] Additionally, other forms of distal brain damage might also be involved in this regard. Diaschisis, the alteration of structural and functional connectivity between brain areas distant from the lesion, is often reported after stroke in both patients and corresponding animal models.[74,75] Diaschisis takes place as early as 24 h after initial injury and persists for weeks. In intracerebral haemorrhage, the rapid intracranial mechanical propagation caused by the haematoma might engender a remote injury, which partly mimics the conditions of brain trauma.[76] This mechanism is supported by the observation of contralateral hemispheric damage post intracerebral haemorrhage.[77] These areas of remote brain damage then might release DAMPs or inflammatory mediators in situ to activate glial cells and recruit leukocytes, further propagating brain inflammation (figure). The molecular spectrum released by remote injured neural cells in global brain inflammation might be distinct from that of focal brain inflammation, which needs future identification.

Neuroinflammation is accompanied by disruption of the blood–brain barrier. Global vascular inflammation and disruption of the blood–brain barrier have been reported in the acute and chronic phases of experimental stroke animal models[60–62] and patients with ischaemic stroke.[40,78] Hence, blood-borne global brain inflammation can be readily induced by microvascular damage (figure). However, the mechanisms underlying global vascular activation are unclear. The interaction of endothelial cells with activated leucocytes[9] and platelets,[79,80] as reported in studies of acute stroke, might represent potential candidates of global vascular activation.

The potential clinical relevance of global brain inflammation

Given the coexistence of global brain inflammation with primary brain injury and focal brain inflammation, distinguishing the pathophysiological role of global brain inflammation during the acute phase is difficult. Nevertheless, evidence suggests that long-lasting global brain inflammation might contribute to chronic

neurodegeneration and affect global brain function after a stroke. Dementia after a stroke occurs in 15–30% of patients with ischaemic stroke.[81] Longitudinal studies posit that several plasma inflammatory markers are predictors of dementia after a stroke, including IL-6, IL-12, erythrocyte sedimentation rate, and C-reactive protein.[81] Furthermore, elevated erythrocyte sedimentation rate is strongly associated with hippocampal volume.[70] These insights suggest the involvement of long-term systemic inflammation in neurodegeneration after a stroke. In a phase 2 trial[82] that included 161 European patients with ischaemic stroke, administration of an α4 integrin monoclonal antibody natalizumab, which inhibits the interaction between endothelial cells and leukocytes during the acute stage of acute ischaemic stroke, improved cognitive and other brain functions at 3 months despite no reduction in infarct volume relative to placebo. Such results suggest that an immune modulatory treatment might improve global brain function in patients with acute ischaemic stroke, possibly through attenuation of global brain inflammation. Depression and fatigue develop commonly in patients who have had a stroke from months to years after disease onset, and some studies[83–85] implicate inflammation in the pathogenesis. Anti-inflammatory medications such as aspirin or statins have been shown to reduce the likelihood of early depression (within 1 year) but conversely increase the risk of late depression,[86] implying that global brain inflammation might play distinct roles during the different stages of stroke recovery.

Cognitive decline also commonly occurs in patients with intracerebral haemorrhage. Although early dementia after intracerebral haemorrhage (≤6 months) is associated with haematoma size and location, delayed dementia (>6 months) is not directly associated with the acute characteristics of intracerebral haemorrhage, and progresses over time.[87] This phenomenon suggests that a secondary biological change that persistently affects brain structure and function occurs in the delayed stage following initial haemorrhage, and global brain inflammation might play a role in this development. In support of this concept, a study[88] examining CT scans in 112 Asian patients at 3 months after intracerebral haemorrhage noted global brain atrophy independent of haematoma location and volume.

With respect to the nature of the immune response after an injury, long-term brain inflammation might also participate in repair and neural network rewiring. However, given the persistence of global brain inflammation alongside progressive neurodegeneration after a stroke, a potentially protective role of global brain inflammation, especially in long-term stage, is less likely.

Conclusion and future perspectives

Despite the different primary injury mechanisms, inflammation is triggered through a common pathway shared by both acute ischaemic stroke and intracerebral haemorrhage, and plays a crucial part in the development of brain oedema and other pathophysiological consequences. Additionally, the evidence reviewed here presents a complex picture of inflammatory responses in the injured brain that are not restricted to the site of injury but which can occur globally and persist in the long term. Global brain inflammation might persistently shape the pathophysiology of brain injury after a stroke and promote decline of global brain functions like cognition. Future research must not only aim to understand how global brain inflammation is initiated and maintained but also clarify the role of global brain inflammation in the long-term sequelae of stroke and its roles in neurological recovery and brain tissue regeneration (panel). These efforts would clear the way for designing immune modulatory therapies to curtail inflammation-associated secondary brain injury.

The recognition of the crucial role of inflammation after stroke has inspired various clinical trials aiming to ameliorate brain inflammation in an effort to counter secondary brain injury during the acute and subacute stages. Although with limited sample sizes in some studies, these trials have yielded encouraging outcomes, and include the evaluation of natalizumab in acute ischaemic stroke,[82] fingolimod in acute ischaemic stroke[89–91] and in intracerebral haemorrhage,[92] and glyburide in acute hemispheric infarction.[93] Several new large-scale clinical trials based on the insights derived from these studies are ongoing (NCT02730455, NCT02864953, NCT03338998, and NCT02956200). Additionally, new genes and molecules responsible for the development of inflammation are being identified from profiling the relevant tissue, such as peri-haematomal tissue derived from patients with intracerebral haemorrhage. The question is whether these genes and molecules can serve as drug targets, and whether there is a so-called master switch that orchestrates the cascade of inflammation. Resolving these issues

Panel: **Future research directions in understanding brain inflammation after stroke**

- Define the factors that trigger and maintain global brain inflammation after a stroke
- Compare the temporal and spatial profile and components (microglia, astrocyte, myeloid cells, lymphocytes, platelets, etc) between global and focal brain inflammation after a stroke
- Identify the common and disease-specific features of brain inflammation among different acute brain injuries and their contribution to disease outcomes, respectively
- Clarify the effect of global brain inflammation on long-term brain structure changes and neurorepair and their associations to clinical outcome
- Search for strategies that can modulate global brain inflammation after a stroke, and test whether these treatments could improve the disease outcome

Search strategy and selection criteria

We searched PubMed for articles published mostly between Jan 1, 2013, and May 31, 2018. We used the terms "inflammation", "neuroinflammation", "immune", "immunity", "ischaemic stroke", "cerebral ischaemia", "haemorrhagic stroke", and "intracerebral haemorrhage". We used English search words, but also included papers published in foreign languages with English abstracts. We selected articles describing clinical and animal model findings on inflammation of stroke.

would be instrumental in designing future therapies for patients with stroke.

The paramount issue is whether a greater understanding of brain inflammation would lead to successful clinical translation of immune modulators for stroke. Previous efforts to manipulate the immune system involved targeting adhesion molecules (ie, natalizumab), cell egress ability (ie, fingolimod), or cytokines in the periphery. These approaches prevent further fuelling of inflammation but do not alter ongoing in-situ processes. Direct interference of molecules that trigger brain inflammation locally is likely to curb injury expansion within the brain. The successful management of patients with stroke might require coupling of focal and systemic approaches to modulate brain inflammation.

Contributors

F-DS, AFD, and MTL formulated the concept. KS, D-CT, and Z-GL searched the articles. All authors drafted the manuscript.

Declaration of interests

We declare no competing interests.

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