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THE POTENTIAL ROLE OF SYSTEMIC IMMUNITY IN STROKE-RELATED COMORBIDITIES

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Anotation

Immunological mechanisms have become a focus of current stroke research, with the modulation of neuroinflammatory pathways identified as a potential therapeutic approach for protecting the ischemic brain. Stroke not only triggers a local neuroinflammatory response, but also has a significant impact on systemic immunity, which is important to consider in the development of new treatments.

In this review, we will discuss the consequences of ischemic stroke on systemic immunity throughout the disease process, from the onset to long-term outcomes. We will also explore the underlying mechanisms of brain-immune communication and the potential role of systemic immunity in stroke-related comorbidities such as cardiac dysfunction, atherosclerosis, diabetes and infections. Finally, we will discuss how targeting systemic immunity after a stroke could improve long-term outcomes and reduce the risk of comorbidities in stroke patients.

Keywords

inflammation, long-term outcome, stroke, systemic immunity

Stroke is a major public health concern with a vast socioeconomic burden. Stroke is also the second leading cause of death and a leading cause of long-term disability worldwide. Despite enormous improvements on diagnosis and therapeutic strategies, the number of incident strokes is expected to more than double by 2050, and the prevalence of long-term disabilities after stroke is anticipated to equally increase due to demographic changes and the growing number of stroke survivors. Stroke can be of ischemic or hemorrhagic nature. Approximately 70% of strokes are ischemic strokes, caused by the occlusion of a major cerebral artery, whereas others are hemorrhagic strokes, characterized by bleedings in the brain substance (intraparenchymal hemorrhages) or the subarachnoid space (SAHs). This review specifically deals with ischemic stroke. At present, treatment interventions for ischemic stroke are limited to acute revascularization strategies, via the administration of thrombolytic agents or through endovascular therapy (catheter-based mechanical thrombectomy). Both types of therapies aim at restoring blood flow to the hypo-perfused brain tissue and need to be applied to patients as early as possible after stroke onset. This narrow therapeutic time window and several medical contraindications seriously reduce the number of stroke patients who currently can benefit from these recanalization therapies; hence, new treatment strategies are still urgently needed. As alternative methods to treat ischemic stroke, many neuroprotective agents have been evaluated during past

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decades to minimize the destructive pathophysiology of stroke and protect the ischemic brain. The vast majority of these treatments target factors participating in the very early processes of ischemic cell death in the affected brain area, which beyond brain cells also comprises a heterogeneous and complex vascular network. Compared to these acute neuroprotective approaches, much less attention has been given to other biological processes that have emerged in recent years as critical pathophysiological processes of stroke, such as systemic inflammation. Systemic poststroke inflammation has been identified as an important determinant of acute and long-term prognosis of stroke patients. As such, systemic inflammation after stroke has become a novel target for translational research. Some first clinical trials aiming to tackle inflammation to minimize patients' functional disabilities and also prevent secondary comorbidities have been already conducted.

On this basis, this review focuses on the consequences of stroke on different branches of the systemic immune response. We will review current knowledge of the systemic changes of the immune system after ischemic stroke and how they might impact on poststroke acquired or pre-existing comorbidities. We will mainly focus on modifiable comorbidities including infections, cardiovascular events, atherosclerosis and diabetes—although other no-modifiable factors such as age and sex can also modulate the inflammatory response to stroke and determine the impact of inflammation on the outcome. Our review will also highlight the increasing and indisputable importance of poststroke systemic immunity on patients' long-term outcome and its potential therapeutic value for the prevention of poststroke adverse events. During past decades, systemic immune changes after stroke were mainly studied in the context of subacute immunosuppression due to its association with the increased susceptibility to bacterial infections in stroke patients. In humans, it is now clear that within the first 12 h after stroke, there is also a pronounced increase in the circulating levels of such pro-inflammatory cytokines, including TNF-α and IL-6; In addition, blood levels of these cytokines have been also positively correlated with stroke severity and unfavorable prognosis of stroke patients.

Beyond the massive release of pro-inflammatory cytokines, leukocytes are also rapidly mobilized from the spleen and the bone marrow, two major reservoirs of immune cells.These cell reservoirs are however limited, and rapidly exhaust within hours after stroke. Thus, at this early time-point after stroke, the bone marrow also increases hematopoiesis to replenish the pool and meet the demand of leukocytes in circulation.Mechanistically, the stroke-induced activation of neurogenic pathways, including the sympathetic innervation, hypothalamic–pituitary–adrenal (HPA) axis and parasympathetic innervation, play a major role in the release of immune cells from these two peripheral reservoirs. It is now known that the observed increase in circulation of norepinephrine and epinephrine levels acutely after stroke contributes to spleen shrinkage and massive exiting of immune cell populations from this organ. Similarly, in the bone marrow, the early activation of sympathetic innervation is observed by an abrupt increase in the levels of tyrosine hydroxylase and norepinephrine within the first day after stroke.The early activation of hematopoietic stem cells proliferation and differentiation has been attributed to this post-stroke increased sympathetic tone. Likewise, in bone marrow mesenchymal stromal cells, activation of β3-adrenergic receptors further results in a downregulation of homeostatic and cell retention factors, including IL-7, C-X-C motif chemokine 12 (also known as stromal cell-derived factor 1), VCAM-1 and angiopoietin-1, which enables the exiting of leukocytes into the bloodstream

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Recent evidence suggests that activated endothelial and circulating innate immune cells after stroke could also promote immunothrombosis, the inflammation-dependent activation of the coagulation system, and thromboinflammation, the aberrant and excessive activation of immunothrombosis . The early activation of the immune system is rapidly followed by a state of systemic immunodepression. The most distinguished feature of this systemic immunosuppressive phase is the reduction in circulating T, B and NK cell counts. In this line, early studies on the immune profile of stroke patients already described profound peripheral lymphopenia as early as one day after ischemic stroke.Therapeutically, a tight regulation of the stroke-induced suppression of cellular immunity could be of clinical relevance for the prevention of post-stroke complications. So far, the lack of success of the β-blocker therapy urges the need for alternative therapies to tackle such life-threatening post-stroke comorbidities. In this regard, because DAMP and other pro-inflammatory cytokines upregulated within the hyper-acute inflammatory response to stroke are also considered to be key triggers of subacute immunosuppression, immunoregulatory approaches mitigating this early pro-inflammatory reaction might ultimately be an alternative promising therapy to limit immunosuppression and poststroke infections. However, to date, no immunomodulation therapy has been clinically tested with the specific endpoint of reducing infections after stroke.

In recent years, the importance of systemic immunity as a key factor in stroke pathology has increased significantly. Despite this growing relevance, there is still no consideration given to systemic inflammation in the management of stroke patients in clinical practice. Strong evidence points to a close connection between post-stroke systemic inflammation and secondary complications, such as infections and various cardiovascular pathologies. This emerging understanding suggests that inflammation may be a potential target for interventions in stroke patients to improve outcomes and prevent secondary complications simultaneously. In particular, targeting interleukin-1β (IL-1β) has shown promising results thus far.

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