Stroke and the Immune System: a Review of the New Strategies

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Abstract

The immunology of stroke can be approached in several ways. By viewing stroke from an immunological standpoint, we are trying to achieve new insights in its pathogenesis and reach new therapeutic options. To review and summarize the findings from publications on immunology of stroke. Infections are a well-known risk factor for stroke. This is due to activated immune cells interacting with thrombocytes and releasing coagulation factors, which affect the formation of the thrombus. Aseptic inflammation in the ischemic lesion leads to cellular invasion of the area and triggers a pro-inflammatory response, which has an impact on further destruction of ischemic brain tissue. Another aspect of stroke is systemic immune suppression, which is a predisposing factor towards a systemic bacterial infection. Infection itself is also an independent risk factor for negative clinical outcomes and increased mortality. The immunological approach to the topic of ischemic stroke holds significant value for future research.

Keywords
alarmins, immunology, inflammation, ischemic stroke, immunomodulation, lymphocytes

INTRODUCTION

Immune response and inflammation are key elements in the pathobiology of ischemic stroke. While immunity contributes to brain damage due to ischemia, the damaged tissue itself triggers a powerful immunosuppressive response, which in turn leads to potentially life-threatening intercurrent infections. Inflammatory signalling is instrumental in all stages of the ischemic cascade. Modulation of the adaptive immune response creates a significant protective effect towards the ischemic brain tissue and offers some new therapeutic options. It is important to keep in mind that immunomodulation can lead to some serious side effects and continuously studying the connections between immunity and ischemic brain damage is essential.

Neuroimmunology of stroke

After a vascular occlusion, a local immune cascade is trig-
cytokines during the different phases of inflammation, among which are the major histocompatibility complex 2 and interleukin 1. This leads to an influx of immune cells through the blood-brain barrier (BBB) and the development of a specific immune response.

**Immune factors**

A number of research papers discuss the ambivalent role of immune factors in the pathogenesis of ischemic stroke. A good example is matrix metalloproteinases. They have been demonstrated to play a part in neuronal damage in the acute phase of stroke. However, experiments on animals demonstrate their role in neurovascular remodeling between day 7 and day 14 after the cerebrovascular incident.

**Lymphocytes**

Lymphocyte subpopulations and T-lymphocytes, in particular, play a key part in the pathogenesis of ischemic stroke. In the acute phase of stroke, T-lymphocytes are unable to pass through the BBB and affect the lesion in an antigen-independent mechanism. Under the effects of oxidative stress and endothelial cell proteases, lymphocytes migrate into the brain parenchyma. They are the main releasers of interferon gamma (INF-Gamma), which is related to neurotoxicity in the late stage of stroke. Gamma-Delta-T-lymphocytes (γδT) and Interleukins 23 and 17 are among the main factors in the development of the cerebral infarction. γδT-cells are activated without the presence of a specific antigen, and in animal models, they infiltrate brain tissue and release INF-Gamma and IL-17. In the same animal models, the depletion of this subpopulation and blocking the aforementioned interleukins leads to a decrease in ischemic damage. In experimental models, the same effect can be achieved through the depletion of CD8+ or CD4+ T-lymphocytes.

**Autoimmune responses**

The contact between the central nervous system (CNS) antigens, which are usually isolated by the BBB, with systemic immunity leads to autoimmune responses after cerebral ischemia. The development of a certain degree of immune tolerance towards CNS antigens is shown to have a protective effect under experimental conditions. In order to avoid the development of a severe autoimmune reaction, it is crucial to maintain a dynamic equilibrium between the pro- and anti-inflammatory factors. In this regard, regulatory T-lymphocytes (T-regs) are of particular importance. These are the specific cellular subpopulations that are responsible for a large part of the modulation of immune response after CNS damage. They mediate both the destruction of inviable cells and the formation of an inflammatory wall that prevents lesion expansion. Regulatory T-lymphocytes are distinguished by the fact that they express CD4, CD25, and FoxP3 on their surface. Their proliferation is stimulated by interleukin-2 (IL2). Out of the three cellular markers, FoxP3 is the one with the highest degree of specificity for T-regs and is proved to have a major role in regulating the level of activity of this specific subpopulation. People having genetic mutations affecting this marker tend to suffer from severe autoimmune diseases. It should be noted, however, that FoxP3 can be found in other subpopulations as well and is thus not 100% specific. After an ischemic stroke, these cells can be found in increased numbers in the spleen in the acute phase, and 5 days after the stroke they can be found in the peri-infarct zone. The numbers of circulating CD4+CD25+ T-regs are higher in stroke patients compared to a healthy control group. Another trial looks into a possible association between increased apoptosis of neurons and decreased numbers of T-regs and other immune cells. The depletion of T-regs in mice with induced cerebral ischemia leads to an increased lesion volume and behavioral pathology. This effect is associated with increased secretion of pro-inflammatory factors, mainly INF-Gamma. The protective effect of T-regs is mediated by IL-10 and is the same as what is observed after intrathecal application of IL-10. Regulatory B-lymphocytes are also linked to a protective effect in ischemic brain damage, which lends further credence to the theory of dynamic equilibrium being necessary for a better outcome after a cerebrovascular incident.

**Autoimmune encephalitis**

Contact between CNS antigens and systemic immunity carries a major risk of autoimmune encephalitis. The release of anti-inflammatory cytokines to prevent such a complication leads to an overall weakening of immunity, which increases the possibility of post-stroke infections. Great importance in this regard is given to some specific T-lymphocyte subpopulations, which demonstrate an anti-inflammatory phenotype under a noradrenergic stimulus.

**Infectious complications**

A meta-analysis of 87 studies including 137,817 patients reports that infectious complications are present in about 30% of stroke patients (95% CI, 24-36%) the major ones being the respiratory and urinary tract infections (UTI). Development of pneumonia after stroke is associated with increased mortality at 30 days (OR 2.2; 95% CI, 1.8-2.7) and the first year (OR 3.0; 95% CI, 2.5-2.7). Nearly half of post-stroke cases of pneumonia occur in the first 48 hours after the incident and almost all cases are within the first week. The presence of dysphagia increases the risk of pneumonia threefold and if there is confirmed aspiration the risk increases 11 times. In another study, there is a report of 16% of patients developing a UTI after stroke; however, there wasn’t a significant correlation between the presence of this complication and overall clinical outcome.
Lesion location and volume

Some studies discuss the possible connection between lesion localization and infectious complications, reporting a higher rate of post-stroke infections in patients suffering from strokes in the anterior part of the middle cerebral artery (MCA) zone and in the insula. Most studies consider lesion volume to be more important than its localization.

Immune suppression

The development of these complications is in itself proof of the presence of post-stroke immune suppression, which is further corroborated by the presence of lymphocytopenia in a percentage of stroke patients quite similar to the percentage that develop post-stroke infections. Adrenergic mediation is of great importance as it is under its effect that the switch from pro-inflammatory TH1 activity towards anti-inflammatory TH2 activity occurs.

Therapeutic implications of the immunology of stroke

Prophylactic usage of antibiotics

One of the main issues in this regard is preventing bacterial infection in stroke patients. In an in-depth analysis of a large number of trials looking into antibiotic prophylaxis after stroke, there is evidence supporting a possible reduction of infectious complications, but with no apparent effect on overall mortality. As a result, a large-scale clinical trial of preventive antibiotic usage after stroke was conducted.\textsuperscript{18,19} It included 2514 patients, randomized into two groups – best medical care only or best medical care and 2g/day of ceftriaxone. Ceftriaxone prophylaxis was not shown to have a marked effect on functional results and also led to a minor increase in adverse reactions (2 cases of C. difficile infection in the Ceftriaxone group) At this point, prophylactic usage of β-lactam antibiotics does not seem to be a promising avenue for preventing post-stroke infections.

Immune-modulation treatment

A novel and quite promising therapeutic possibility is immune-modulation treatment in stroke patients, based upon improved insight into the immune-pathogenetic mechanism at work during ischemic brain damage. Based on data from research on cellular cultures and animal models, several different clinical trials were conducted.

Tetracyclines

One of these trials\textsuperscript{20} included 152 stroke patients, age>18, NIHSS>5, between 6 and 24 hours after the incident. Excluded were patients less than 6 hours from the incident, those allergic to tetracyclines, patients with intracerebral hematoma, dysphagia, acute or chronic renal failure. Seventy-four of the patients received 200 mg/d of minocycline in addition to their standard medical care and therapy. There was a significant reduction in NIHSS score at 90 days in the minocycline group (1.6±1.9 vs. 6.5±3.8 for the control group, p<0.0001). This difference was present from the first day of the trial and persisted throughout the entire 90-day period. This is considered to be due to minocycline’s suppressive effect on microglial activity and glutamate excitotoxicity, which is demonstrated both in vitro and in animal models. Minocycline also shows inhibitory activity toward metallopeptinases and T-cell proliferation. Due to the likely mechanism of action being suppression of apoptotic cascade, minocycline has a therapeutic window of about 24 hours after the incident which is the time at which apoptosis peaks after a stroke. The success of this trial led to two additional trials on a larger scale. The first of them was Minocycline to Improve Neurologic Outcome in Stroke (MINOS)\textsuperscript{21}, which tested the safety of intravenous application of Minocycline in dosages of 3, 4, 5, 6, or 10 mg/kg/day over a period of 72 hours. This trial included 60 patients within the first six hours after stroke. Of these, 41 received the maximum dosage of minocycline and 60% received intravenous thrombolysis. Infusion of minocycline was well tolerated and there were no severe hemorrhagic complications. Plasma half-life was determined to be about 24 hours. The results demonstrated a good level of safety in the tested dosage and application method. These positive results led to a multicentric clinical trial of the efficiency of minocycline in improving functional outcomes after stroke.\textsuperscript{22} In this trial oral minocycline was compared to placebo over a 5-day period. This large-scale trial failed to prove a significant difference in outcome between patients given minocycline and patients given placebo.

Blocking neutrophil activity

Another therapeutic approach is blocking neutrophil activity using a recombinant neutrophil-inhibiting factor.\textsuperscript{23} This molecule demonstrates a reduction in neutrophil infiltration and lesion volume in animal models. A double-blind, randomized clinical trial comparing this molecule in 16 different dosages with placebo was conducted on a group of 966 stroke patients. There were neither any serious adverse effects nor a significant difference in outcome compared to placebo.\textsuperscript{24}

Blocking intracellular adhesion molecule 1

Another potential therapeutic strategy is blocking intracellular adhesion molecule 1. A murine monoclonal antibody, targeting this molecule was developed under the name of enlimomab.\textsuperscript{25} After a dosage-determining trial, a conclusion was reached that dosages of 140 mg to 480 mg over a 5-day period don’t lead to severe adverse reactions. A loading dose of 160 mg, followed by 4 doses of 40 mg was selected for use in future trials.\textsuperscript{26} This regimen was utilized in a following clinical trial. 625 patients with ischemic stroke were randomized into two groups – 317 for a 5-day treatment with enlimomab in the above dosage and 308 were given a placebo. The results were very negative in the enlimomab group – a significantly worse functional status.
as rated with the modified Rankin Scale (mRS) at 90 days, fewer patients making full recovery, greater mortality and significantly more adverse events. Later trials demonstrated that infusion of heterologous antibodies after ischemic stroke led to ischemic zone expansion. It is possible that this adverse effect is due to the formation of anti-mouse antibodies and neutrophil activation via the complement system.

**Blocking the α4-β1 integrin of leukocytes**

Another possible approach to immunomodulation in stroke is blocking the α4-β1 integrin of leukocytes. To test this hypothesis, a randomized clinical trial was conducted comparing natalizumab with placebo. The trial was based on animal model research. The intravenous application of 300 mg of natalizumab did not have a significant effect on the ischemic lesion growth observed on MRI at days 1, 5 and 30.

**Sphingosine-1-phosphate receptor modulation**

A much more promising option is treatment with fingolimod. It is a sphingosine-1-phosphate receptor modulator, that has demonstrated an excellent degree of safety and effectiveness in the treatment of multiple sclerosis. Fingolimod was tested in two clinical trials in China. One of them included 22 patients who did not fulfill the criteria for revascularization treatment. They were divided into 2 groups – one received standard medical care and the other standard care and 0.5 mg/day of fingolimod for 3 days. After the first week, the control group had an increase in NIHSS mean scores from 9 to 10, while the fingolimod group had a reduction from 11 to 7 points. This is a significant difference (4±0.3 compared to -1±0.4, p=0.0001). The difference is especially pronounced in patients with larger occlusions compared to those with lacunar infarcts. At 90 days, in the fingolimod group were observed significant differences in NIHSS (1.7±0.8 compared to 5.8±1.7, p=0.02), Modified Barthel Index (mBI) (62±11 compared to 87±8, p=0.0049) and mRS 0-1 (0% for the control group and 73% for the fingolimod group). There was also a notable positive effect on lesion volume on day 8. A decreased number of circulating lymphocytes was observed over the entire trial period in the group treated with fingolimod. In a later clinical trial with 47 participants, the combination of alteplase and fingolimod was compared to alteplase only. Twenty-five patients received the combined treatment and 22 received the classic intravenous thrombolysis. The patients were aged 18-80 years, had a NIHSS>5, no contraindications for thrombolysis, no dysphagia, did not take any other cytostatic or immunosuppressive medication. In this trial, there was also a decreased number of circulating lymphocytes, a smaller lesion volume (10.1 ml compared to 34.3 ml; p=0.04), fewer hemorrhagic complications and a lower NIHSS scores (4 vs. 2; p=0.02) on the first day. At 90 days the researchers observed a better mRS score (73% rated 0-1 compared to 32% in the control group) and a lesser degree of lesion expansion (2.3 ml compared to 12.1 ml; p<0.01). Fingolimod was also tested on patients with intracerebral hemorrhage. The trial included 23 patients with intracerebral hemorrhage with a volume of 5-30 ml. All patients were given medical care according to international standards and some of them also received 0.5 mg of fingolimod orally for 3 consecutive days. The patients treated with fingolimod had better results on the Glasgow Coma Scale (GCS) (15 points for 100% of the fingolimod group compared to 50% of the control group; p=0.01), NIHSS (a reduction of 7.5 points compared to 0.5 points for the control group; p=0.01) and mRS (0-1 for 63% of the fingolimod group compared to 0% of the control group; p=0.001). This trial also noted a smaller number of circulating lymphocytes. This reduction in the number of circulating lymphocytes seems to be the main difference between the effect of fingolimod and natalizumab on stroke patients and at this time it can be inferred that it plays a major part in the differing effects of their usage in stroke patients.

**CONCLUSION**

The immunological aspects of the pathogenesis of ischaemic stroke are a promising new avenue for a therapeutic approach to this very important medical issue. The better insight into the underlying immune processes will undoubtedly bring to light many additional elements of the pathogenic cascade, which, if controlled, can help achieve a better clinical outcome and recovery. At the same time, improved understanding of the dynamic equilibrium between proinflammatory and anti-inflammatory factors will allow a better prediction of some of the non-vascular complications after stroke, some of the most important among which are the post-stroke infections leading to increased mortality and worsened recovery.

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**Conflict of Interests**

The authors declare that no competing interests exist.
### Table 1. Summary of clinical trials for immune-modulation treatment of ischemic stroke

| Drug                        | Mechanism                                                                 | Trial                                                                 | Trial Design                                                                                   | Route of administration and dosage | Outcome                                                                                           | Sources                        |
|-----------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------|--------------------------------------------------------------------------------------------------|--------------------------------|
| Minocycline                 | Suppression of microglial activity; Inhibition of metalloproteases and T-cell proliferation; Suppression of apoptotic cascade | Minocycline treatment in acute stroke.                               | Open-label evaluator-blinded study of 152 patients 6-24 h after stroke                       | 200 mg p.o. for 5 days              | Significant reduction in NIHSS at 90 days; No increase in adverse events.                          | Y Lampl et al.20               |
|                            |                                                                           | Minocycline to improve neurologic outcome in stroke (MINOS)          | A dose-finding study of 60 patients <6 h after stroke. 41 received the highest dose. 60% received concurrent r-tPA. | 3, 4, 5, 6 or 10 mg/kg i.v. over 72 h | Infusion well-tolerated. Plasma half-life ~24h; No severe hemorrhagic complications.             | SC Fagan et al.21              |
|                            |                                                                           | Neuroprotection with minocycline therapy for acute stroke recovery trial (NeuMAST) | A multi-center randomized, double-blind, placebo-controlled trial. 139 patients 3-48 h after stroke | Per os for 5 days                   | No significant effect on mRs, NIHSS, Barthel index at 90 days; No serious adverse reactions.     | SingleAth Foundation22          |
| Recombinant neutrophil-inhibiting factor (UK-279,276) | Blocking neutrophil infiltration of the site of infarction by CD11b/CD18 receptor inhibition. | Acute stroke therapy by inhibition of neutrophils (ASTIN)           | Double-blind, placebo-controlled adaptive dose-response study of 966 acute stroke patients, 887 ischemic, 204 co-treated with r-tPA. | A single dose of 10-120 mg.            | No effect on DeltaSSS. No serious adverse reactions.                                           | M. Krams et al.24               |
| Enlimomab                   | Murine antibody Blocking Intracellular adhesion molecule 1.                | Enlimomab acute stroke trial (EAST)                                  | A double-blinded, placebo-controlled trial with 625 patients                                     | 160 mg loading dose + 4 doses of 40 mg | Higher mortality, mRS, NIHSS and lower Barthel Index, and symptom-free recovery in the enlimomab group; More serious adverse events in the enlimomab group | EAST Investigators27            |
| Natalizumab                 | Blocking the α4-β1 integrin of leukocytes.                                | ACTION                                                               | A double-blinded, placebo-controlled trial with 161 patients 0-9 h after stroke                | 300 mg intravenous single dose       | No significant effect on lesion growth on MRL.                                                   | J Elkins et al.30              |
| Fingolimod                  | Spingosine-1-phosphate receptor antagonist. Reduced egress from lymph nodes of cells expressing this receptor. | Impact of immune modulator fingolimod on acute ischemic stroke      | Open-label, evaluator-blinded trial with 22 patients >4.5 h after stroke                       | 0.5 mg/d per os for 3 consecutive days | Better scores on NIHSS, mBI, and mRS at 90 days in the fingolimod group. Decreased lesion volume and number of circulating lymphocytes in fingolimod group   | Y Fu et al.33                  |
|                            |                                                                           | Combination of the immune modulator fingolimod with alteplase in acute ischemic stroke | Multicenter, open-label, evaluator-blinded trial of 47 patients <4.5 h after stroke indicated for intravenous thrombolysis | 0.5 mg/d per os for 3 days in addition to r-tPA | Better scores on NIHSS and mRS at 90 days in the fingolimod group. Decreased lesion volume and number of circulating lymphocytes in fingolimod group. No significant increase in adverse events. | Z Zhu et al.34                  |
|                            |                                                                           | Fingolimod for the treatment of intracerebral hemorrhage              | 2-arm, an evaluator-blinded study of 23 patients with primary intracerebral hemorrhage.        | 0.5 mg per os for 3 days             | Better results on GCS, NIHSS, and mRS for the fingolimod group.                                  | Y Fu et al.35                  |
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Инсульт и иммунная система: обзор новых стратегий

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Резюме

К иммунологии инсульта можно подойти с разных точек зрения. Рассматривая инсульт с иммунологической точки зрения, мы пытаемся прийти к новым выводам, связанным с его патогенезом, и найти новые терапевтические возможности. Рассмотреть и обобщить данные из публикаций по иммунологии инсульта. Инфекции являются хорошо известным фактором риска развития инсульта. Это связано с тем, что активированные иммунные клетки взаимодействуют с тромбоцитами и высвобождают факторы свертывания, которые влияют на образование тромба. Асептическое воспаление в ишемическом поражении приводит к клеточной инвазии в область и вызывает провоспалительный ответ, который влияет на дальнейшее разрушение ишемической ткани мозга. Другая сторона инсульта – системная иммуносупрессия, которая является предрасполагающим фактором для системной бактериальной инфекции. Сама инфекция также является независимым фактором риска отрицательных клинических исходов и увеличения смертности. Иммунологический подход к теме ишемического инсульта имеет важное значение для будущих исследований.

Ключевые слова

алармины, иммунология, воспаление, ишемический инсульт, иммуномодуляция, лимфоциты