Increasing evidence shows that the central nervous system and the immune system interact in complex ways, and better insight into these interactions may be relevant to the treatment of patients with stroke and other forms of central nervous system injury. Atherosclerosis, autoimmune disease, and physiological stressors, such as infection or surgery, cause inflammation that contributes to vascular injury and increases the risk of stroke. In addition, the immune system actively participates in the acute pathogenesis of stroke. Thrombosis and hypoxia trigger an intravascular inflammatory cascade, which is further augmented by the innate immune response to cellular damage occurring in the parenchyma. This immune activation may cause secondary tissue injury, but it is unclear whether modulating the acute immune response to stroke can produce clinical benefits. Attempts to dampen immune activation after stroke may have adverse effects because central nervous system injury causes significant immunodepression that places patients at higher risk of infections, such as pneumonia. The activation of innate immunity after stroke sets the stage for an adaptive immune response directed against brain antigens. The pathogenic significance of adaptive immunity and its long-term effects on the posts ischemic brain remains unclear, but it cannot be ruled out that a persistent autoimmune response to brain antigens has deleterious and long-lasting consequences. Further research will be required to determine what role, if any, immunity has in long-term outcomes after stroke, but elucidation of potential mechanisms may open promising avenues for the development of new therapeutics to improve neurological recovery after brain injury.

Mounting evidence indicates that the immune system has a key role in brain injury. A better understanding of the interactions between the immune system and the brain can aid physicians who care for patients with stroke and other forms of central nervous system (CNS) injury. In addition, advancing our understanding of the immunology of stroke promises to generate novel clinical strategies, as well as diagnostic and therapeutic approaches. In this brief review, we discuss selected aspects of the interactions between CNS injury and immunity, focusing on its implications for new diagnostic tools to identify patients at risk of stroke and the potential for novel therapeutic agents to modify the immune response to stroke. In addition, we highlight the many gaps in our understanding of the role of the immune system in CNS injury and examine promising avenues of future investigation. Although relevant to the concept of immunity and stroke, primary and secondary CNS vasculitides fall outside the scope of this brief overview and will not be discussed.

IMMUNE ACTIVATION AND THE RISK OF STROKE

Several lines of evidence suggest that activation of the immune system may increase the risk of stroke (Table). Numerous pro-
notoriously prone to confounding, and animal models of stroke in these patients. However, observational data are insufficient to determine whether immunomodulatory agents as new tools to prevent inflammation and atrial fibrillation. Such treatment may prevent atherosclerosis, with a causal role in the pathogenesis of atrial fibrillation. Prevention strategies that target inflammation reduce the risk of stroke. Understanding the link between inflammation and stroke may lead to better and more timely recognition of specially vulnerable subgroups who derive greater or lesser degrees of benefit from standard medications, such as antiplatelet or lipid-modifying agents. In addition, improved knowledge about the link between inflammation and stroke may lead to better and more timely recognition of specially vulnerable populations, such as patients with recent infection or surgery who face a transiently heightened risk of stroke. These patients may be at increased risk from inappropriate cessation of antithrombotic medications, and recognition of their vulnerability to stroke will help to ensure that antithrombotic drugs are stopped only if absolutely necessary and as briefly as possible.

The association between stroke and antecedent inflammatory states, such as infection or surgery, complements recent findings of a correlation between stroke and the duration of chronic inflammatory diseases, such as systemic lupus erythematosus and rheumatoid arthritis. The increased risk of stroke and coronary artery disease seen in patients with lupus seems to be out of proportion to traditional vascular risk factors, implying an additive effect of underlying inflammation. Furthermore, animal models demonstrate that atherosclerosis has an inflammatory component, and inhibition of the immune response to lipoproteins seems to reduce the progression of atherosclerosis. These observations suggest that inflammation may have a causal role in vascular injury and subsequent stroke, which would open the door for immunomodulatory agents as new tools to prevent stroke in these patients. However, observational data are notoriously prone to confounding, and animal models often do not apply well to humans. Clearly, a more detailed understanding of the complex relationship between inflammation and stroke is required to better assess the feasibility of immunomodulation as a potential tool for stroke prevention.

Inflammation is increasingly recognized as a potential pathway in the pathogenesis of atrial fibrillation, which is a leading cause of stroke. Levels of C-reactive protein are elevated in patients with atrial fibrillation and are associated with incident atrial fibrillation and with its recurrence after ablation or cardioversion. Inflammatory pathways may promote atrial fibrillation by interacting with cell signaling cascades, causing ion channel dysfunction, impairing myocyte gap junctions, promoting atrial fibrosis, and recruiting leukocytes to cardiac tissue. The relationship between inflammation and atrial fibrillation is most likely bidirectional, with atrial fibrillation causing some degree of immune activation and inflammation. The prothrombotic state seen in atrial fibrillation may reflect this inflammation, and anticoagulation with heparinoids seems to reduce biomarkers of inflammation in patients with atrial fibrillation. On the other hand, perioperative treatment with glucocorticoids reduces the incidence of atrial fibrillation after cardiac surgery, which suggests that inflammation may also have a causal role in the pathogenesis of atrial fibrillation. Once patients develop atrial fibrillation, their risk of stroke varies in proportion to known clinical risk factors, such as congestive heart failure, hypertension, age, diabetes mellitus, prior stroke, and peripheral vascular disease. However, levels of the proinflammatory cytokine interleukin 6 are also associated with stroke risk, suggesting that inflammation is an additional biomarker of stroke risk within this population. Given these data, physicians should be mindful that periods of heightened

<table>
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<tr>
<th>Table. Examples of Brain-Immune Interactions and Their Clinical Implications in the Care of Patients With Stroke</th>
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<td><strong>Examples</strong></td>
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<td>Biomarkers of stroke risk include white blood cell count, fibrinogen, D-dimer, and C-reactive protein. Duration of systemic lupus erythematosus and rheumatoid arthritis correlates with risk of stroke. A transient increased risk of stroke occurs after infection or surgery. A link exists between inflammation and atrial fibrillation.</td>
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<td>Intravascular hypoxia from thrombosis activates complement and endothelial cells. Oxidative stress reduces nitric oxide, promoting platelet and leukocyte aggregation. Platelet activation generates proinflammatory signals. Spread of inflammation into perivascular space activates resident macrophages. Dying cells release signals that promote inflammation. Loss of neurons removes the anti-inflammatory check on adjacent microglia.</td>
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<td>Stroke results in lymphopenia, upregulation of anti-inflammatory cytokines, and splenic atrophy. Pneumonia and urinary tract infections occur frequently after stroke. Cortisol and catecholamine levels correlate with susceptibility to infection after stroke.</td>
</tr>
<tr>
<td>Inflammatory brain infiltrates persist for years after stroke. Abnormal blood-brain barrier permeability may be associated with radiographic white matter disease.</td>
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inflammation (such as acute medical illness or recent surgery) place patients at higher risk of atrial fibrillation and stroke. With further development, biomarkers of inflammation may help to stratify patients’ risk of developing atrial fibrillation and stroke, allowing targeted screening, risk factor modification, and timely treatment. A better understanding of the interactions among atrial fibrillation, inflammation, and thromboembolism may lead to the development of therapeutic agents that modulate inflammatory pathways to reduce the risk of atrial fibrillation and stroke.

**IMMUNE SIGNALING DURING ACUTE INFARCTION**

Besides its background role in stroke risk, the immune system actively participates in the acute pathogenesis of stroke (Figure). Independent of any immune response, brain ischemia quickly causes failure of ion pumps, overaccumulation of intracellular sodium and calcium, loss of membrane integrity, and necrotic cell death. In addition, arterial occlusion immediately leads to intravascular hypoxia, changes in shear stress, and the production of reactive oxygen species, all of which in turn activate the coagulation cascade, complement, platelets, and endothelial cells. This results in a vicious cycle, with fibrin formation entrapping platelets and leukocytes and causing further vascular occlusion. oxidative stress reduces the bioavailability of nitric oxide, undermining its protective role in promoting vasodilation and inhibiting platelet aggregation and leukocyte adhesion, causing further vascular occlusion and ischemia. Central in this cascade of events is the translocation of P-selectin, an adhesion molecule whose expression on the surface of platelets and endothelial cells rapidly leads to cell adhesion. Trafficking of inflammatory cells into the perivascular space is facilitated by down-regulation of junctional proteins that maintain the integrity of the endothelial lining and the blood-brain barrier. Involvement of the perivascular space then activates resident macrophages and mast cells, leading to the release of vasoactive mediators and proinflammatory cytokines, which in turn recruit and promote the infiltration of more leukocytes.

As cells die of ischemia, they release signals that further activate the immune system. Extracellular accumulation of adenosine triphosphate released from dying cells activates microglia, which develop characteristics of macrophages and release proinflammatory mediators. Numerous normally intracellular components serve as danger-associated molecular pattern molecules on their release from dying cells, and these molecules activate toll-like receptors and scavenger receptors on microglia, perivascular macrophages, dendritic and endothelial cells, and infiltrating leukocytes. This activation induces the expression of proinflammatory molecules and primes dendritic cells for antigen presentation. Such proinflammatory changes are initially counterbalanced by the release of neurotransmitters, which activate anti-inflammatory receptors on microglia, and by the presence of cell-cell interactions between microglia and adjacent neurons, which usually keep microglia quiescent. However, as ischemic cell death progresses, neurons die and neurotransmitters are depleted, releasing this brake on proinflammatory signaling.

The clinical implications of the immediate immune involvement in the ischemic cascade are unclear. On the face of it, proinflammatory signals seem to promote mi-
crovascular occlusion and should tend to increase the size of the resulting infarct. In fact, in experimental models of stroke, mice deficient in adhesion receptors or complement subunits seem to be protected from acute ischemia, and healthy mice treated with inhibitors of adhesion molecules or the complement cascade also develop less ischemic brain injury. In addition, mice engineered to lack selected T-cell subgroups are protected from ischemic damage to the penumbral zone around areas of infarction. Available data indicate that the protective effect of lymphocyte suppression does not stem from an inability to propagate thrombus and that no significant differences in cerebral blood flow exist between healthy and lymphocyte-deficient mice. It is possible that lymphocytes instead produce cell damage directly or through proinflammatory signaling and activation of downstream microglia and macrophages. Or, the early damage associated with lymphocyte infiltration of the ischemic brain may be due to the natural killer T-cell subtype that harbors a simplified T-cell receptor and may not require antigen processing. The available data do not provide a clear picture of how lymphocytes participate in acute infarction.

Clinical attempts to explicitly modify the immune response after stroke (such as trials of recombinant neutrophil inhibitory factor or antibodies against adhesion molecules) have been ineffective to date, and these failures highlight the complexity and redundancy of the pathways involved in the immune response to stroke. On the other hand, observational data and a randomized clinical trial indicate that acute use of statin medications at the time of stroke improves long-term outcomes and reduces mortality. Because this time window is not consistent with the lipid-lowering effects of statin medications, the benefit of their use during the acute stage of stroke has been attributed to their anti-inflammatory properties. This suggests that, despite the absence of specific clinical strategies or drugs proven to beneficially modulate immune functioning during acute brain infarction, further elucidation of this complex interplay may yield more sophisticated and pleiotropic therapeutics to augment the limited repertoire of antithrombotic agents available to physicians today.

THE ROLE OF ADAPTIVE IMMUNITY AFTER STROKE

The inflammatory processes detailed thus far occur in a short time window after infarction and rely on the innate immune system, which involves the rapid activation of low-affinity receptors that recognize a wide range of targets. The immediate onset of this inflammatory cascade and the available experimental data on patterns of signaling during early immune activation do not support a substantial role in this process for the adaptive immune system, which relies on the clonal expansion of specific lymphocytes with high-affinity receptors to specific antigens. However, the general immune activation caused by cerebral ischemia raises the questions of whether the adaptive immune system is eventually activated and how it may contribute to the propagation and repair of brain injury after stroke.

After stroke, the number of antigen-presenting cells in the brain increases, along with costimulatory molecules required for antigen presentation to lymphocytes. This antigen presentation results in the production of antibodies against brain antigens and T cells sensitized to brain antigens. Furthermore, successive mucosal administration of myelin antigens in experimental models results in the development of immune tolerance and protection from subsequent ischemic injury, suggesting that this immune response involves adaptive immunity and that modulating it may be protective. On the other hand, although lymphocyte-deficient mice are protected from ischemic brain damage, reconstituting them with T cells directed against non-CNS antigens worsens ischemic damage. In addition, mice lacking the necessary costimulatory molecules for antigen-specific T-cell responses are nevertheless vulnerable to ischemic damage. Therefore, it is unclear whether the release and presentation of CNS antigens during and after stroke result in an adaptive immune response directed against the CNS.

If such an autoimmune response was directed against the brain after stroke, its long-term implications would potentially be significant (Table). Such immune activity would be expected to impair neuronal plasticity and functional recovery and contribute to the frequent incidence of poststroke dementia. Such concerns are supported by the presence of inflammatory infiltrates in damaged areas of the brain years after stroke, as well as by persistently elevated titers of antibodies to brain antigens. Abnormal permeability of the blood-brain barrier has been linked to the radiographic white matter changes frequently associated with vascular disease and cognitive decline, and levels of inflammatory biomarkers such as C-reactive protein are associated with white matter changes, lacunar strokes, and loss of microstructural integrity as measured by diffusion-tensor imaging. Therefore, it cannot be discounted that immune activation contributes to the alterations in this endothelial permeability and vascular dysfunction. On the other hand, immune cells such as microglia may be important for clearing deleterious cellular debris that can cause neurodegeneration. Further research will be required to determine what role, if any, immunity has in long-term outcomes after stroke, but elucidation of any potential mechanisms may open promising avenues for the development of new therapeutics to improve neurological recovery after brain injury.

RESOLUTION OF INFLAMMATION AND THE ROLE OF THE IMMUNE SYSTEM IN TISSUE REPAIR

The inflammation unleashed by cerebral infarction is followed by a carefully orchestrated process to clear necrotic debris and foster tissue repair. This reparative process releases mediators that actively bring the inflammatory process to a close. Phagocytosis of dead cells by microglia and macrophages promotes the production of immunomodulatory cytokines, such as transforming growth factor β and interleukin 10. Although transforming growth factor β has numerous proinflammatory effects, in this context it helps to suppress inflammation by inhibiting helper T-cell responses and promoting regu-
latory T-cell development. Interleukin 10 has neuropro-
tective and anti-inflammatory properties, and its release
helps to facilitate the resolution of inflammation and pro-
motes the survival of remaining viable neurons.

In this evolving process, the same cells that were ini-
tially recruited in the inflammatory phase serve as im-
portant sources of growth factors required for neuronal
sprouting, neurogenesis, angiogenesis, gliogenesis, and
matrix reorganization. For example, microglia are re-
quired for the full expression of insulinlike growth fac-
tor 1, which promotes neuronal sprouting after injury.
Reactive astrocytes produce vascular endothelial growth
factor, which is required for angiogenesis. Circulating
CD34⁺ immune progenitor cells promote revasculariza-
tion in infarcted brain tissue. This reparative aspect of
immune cells raises expectations that they can be har-
nessed to augment neuronal repair and recovery after CNS
injury. However, experimental efforts so far provide cau-
tionary tales; for example, increasing vascular endothe-

dial growth factor levels early after ischemia or in exces-
sive amounts actually worsens injury. Such findings
highlight the complexity of the immune response to CNS
injury and indicate that attempts to modify these inter-
actions must be undertaken with care.

**BRAIN INJURY AND IMMUNOSUPPRESSION**

Thus far, we have focused on the effects exerted by the
immune system on the CNS after stroke. However, this
interaction is bidirectional, and CNS injury has pro-
found effects on immune function (Table). Within days
of stroke, patients develop significant immunodepres-
sion, marked by lymphopenia, upregulation of anti-

flammatory cytokines, and splenic atrophy.⁸ This im-
munodepression clinically manifests in the high rate of
systemic infections seen in the immediate poststroke pe-
riod. Patients with stroke are especially at risk of pneu-
monia and urinary tract infections, and such infections
may independently worsen neurological outcomes and
increase mortality. Immunodepression may account for
the inability of other factors (such as dysphagia) to fully
account for the high rates of pneumonia seen in surviv-
ors of stroke.

Poststroke immunodepression seems to be mediated
by catecholamines and steroids released by sympathetic
activation after stroke. Cortisol and serum catechol-
amine levels correlate with susceptibility to infection af-
ter stroke, and experimental models have shown that ste-
droid and adrenergic antagonists counteract lymphocyte
apoptosis and reduce rates of infection after brain in-
jury. Intriguing clinical observations associate β-blocker
use with lower rates of pneumonia and mortality after
stroke,⁹ but given the sparse nature of these data and the
pleiotropic effects of β-blockers, further research will be
required to determine the usefulness of such widely avail-
able drugs to modulate the immune response after stroke.

Other efforts to counteract poststroke immunode-
pression have involved the prophylactic administration
of antibiotics after stroke to protect patients from com-
mon infections. Several randomized trials investigated
whether this strategy improves outcomes after stroke, and
a meta-analysis¹⁰ of their results indicates that antibi-
otic use reduced the rate of infections but not mortality.
However, these studies were underpowered to detect a
meaningful difference in mortality rates, and further large
trials will be required to answer this question. If antibi-
otic use is eventually shown to improve outcomes after
stroke, questions will remain about the effects of such a
strategy on microbial resistance patterns. Nevertheless,
it is possible that a strategy of prudent poststroke anti-
biotic use may emerge as a cost-effective and safe strat-
gy for improving outcomes in these vulnerable pa-
tients. In the meantime, physicians should be cognizant
of the immunosuppressed state of their patients with
stroke and should remain vigilant to expeditiously iden-
tify and appropriately treat infections in these patients.

**RELATIONSHIP BETWEEN POSTSTROKE
IMMUNODEPRESSION AND ADAPTIVE IMMUNITY**

In speculating about why poststroke immunodepres-
sion occurs, on the surface it would seem to harm pa-

tients by increasing their risk of infectious complica-
tions. Although it may simply be a maladaptive response
that stems from inherent aspects of the design of the CNS
and immune system, immunodepression may serve to pro-
tect the CNS from the development of adaptive immune
responses directed against self. Recent data indicate that
the CNS undergoes regular immune surveillance by cir-
culating lymphocytes. Central nervous system compo-

nents are not routinely presented to these lymphocytes
in such a way as to sensitize them and launch an im-
mune response against the CNS. However, in the ab-


ence of countervailing factors, such antigen presenta-
tion would be expected to occur after CNS injury and
and compromise of the blood-brain barrier. Therefore, the
immunodepression seen after stroke may serve a benefi-
cial purpose in limiting the development of such auto-
immunity. Such considerations suggest that a detailed
understanding of the many facets of the interactions be-
tween the CNS and the immune system is needed to guide
any interventions to modify these interactions and im-
prove outcomes.

**CONCLUSIONS**

The relationship between the CNS and the immune sys-

tem is complex and remains incompletely understood.
It has particular salience after stroke and other forms of
CNS injury, which trigger immune processes that seem
to be both beneficial and harmful. A major frontier in
stroke research involves efforts to better understand these
interactions to develop new strategies and drugs that will
prevent and reduce the burden of stroke. Based on cur-
rent knowledge, physicians should be mindful that un-
derlying inflammation is a biomarker of stroke risk and
should carefully consider antithrombotic, statin, and an-
tihypertensive therapy in vulnerable populations. Fur-
ther work will be needed to delineate precise clinical strat-
egies for risk factor modification based on specific biomarkers. In addition, it would be reasonable to ad-
minister statin drugs to patients with acute stroke given
data suggesting that this improves outcomes, possibly as
a result of anti-inflammatory properties. Furthermore,
physicians caring for patients with stroke should recognize that poststroke immunodepression increases the risk of infection and should adjust their clinical suspicion and treatment strategies accordingly. Whether a strategy of routine prophylactic antibiotic administration after stroke is beneficial remains unknown, but it holds promise as a simple method for improving poststroke outcomes. Finally, the care of patients with stroke may be improved by advances in specific areas, including investigation of whether modulating inflammatory pathways can reduce the risk of stroke and decrease penumbral ischemia during acute stroke, whether immunity has a role in poststroke functional recovery and dementia, and whether strategies to prevent poststroke immunodepression can reduce the incidence of infection after stroke without increasing dangerous autoimmunity against the brain. The immune system has not traditionally been the subject of therapeutic manipulation in patients with stroke, but given its intertwined relationship with the CNS, it promises to be an exciting avenue for future attempts to reduce the high burden of disability and death from stroke.

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