Disability and death after ischemic stroke continue to represent an enormous health and economic burden worldwide. Alarming, pharmacological treatment options for patients with acute stroke are still limited to just the clot-buster agent, recombinant tissue-type plasminogen activator, which must be administered within 4.5 hours of symptom onset and only after a computed tomography scan has confirmed the cause to be a thrombus rather than a hemorrhage. Hence, because of these challenging timing constraints, the majority of patients with stroke receive no meaningful interventional treatments to limit injury or promote healing besides those designed to prevent a secondary ischemic event (eg, antplatelet and antihypertensive agents).

This continuing lack of useful targeted therapies for acute stroke is, in part, because of our still poor understanding of the enormous complexity of cellular and molecular mechanisms that are triggered within and outside of the brain during the hours and days after cerebral ischemia. To develop effective stroke therapies, we need to first unravel and identify detrimental mechanisms and their relevant timing from others that are beneficial or neutral in terms of influencing a patient’s ultimate functional outcome.

Primary neuronal injury and death, which occur in the core of ischemic brain tissue, caused by hypoxia and neurotoxicity within just a few minutes of blood flow interruption, cannot realistically be halted in the clinical setting. Secondary neuronal injury, however, resulting in large part from inflammation of the postischemic brain during several days, probably also contributes substantially to the ultimate magnitude of ischemic brain damage and perhaps could be clinically targeted. Specifically, such secondary injury will likely impact the penumbra, a region of threatened and functionally silent brain tissue surrounding the infarct core, which theoretically could still be salvaged by an appropriately targeted intervention but also could be mortally injured by inappropriate attack by inflammatory cells.

Our understanding of the temporal and spatial inflammatory changes in the postischemic brain is still incomplete, but the process seems to involve the infiltration of numerous types of innate and adaptive immune cells in widely differing numbers and timeframes. Of particular prominence are neutrophils, monocytes/macrophages, and T lymphocytes, which first interact with cerebral endothelium and other immune cells via various adhesion molecules to undergo activation and extravasation—a process coordinated by a myriad of proinflammatory chemokines generated locally by the damaged tissue. The migration of leukocytes through the cerebral endothelium is facilitated by disruption of the blood–brain barrier (BBB). This is caused by enzymatic degradation of the perivascular extracellular matrix by matrix metalloproteinases (MMPs), including MMP-9 released from infiltrating neutrophils early after stroke. It is critical that we gain a better understanding of the link between BBB breakdown and activation of immune cells because the brain swelling caused by edema that occurs as a result of the loss of BBB integrity represents a major threat to patient survival after acute stroke. Any newly identified mechanism that could impact poststroke BBB function, either positively or negatively, therefore may represent a novel target for therapy via promotion or inhibition, respectively.

Carcinoembryonic antigen–related cell adhesion molecule 1 (CEACAM1), a member of the immunoglobulin superfamily, is highly expressed on neutrophils and endothelial cells, and it is known to control neutrophilic granulocyte function during bacterial infections. Unlike classical proinflammatory cell adhesion molecules (eg, intercellular adhesion molecule 1 [ICAM 1] and vascular cell adhesion molecule 1 [VCAM 1]), CEACAM1 is an inhibitory immune coreceptor that suppresses signal transduction, and that is known to bind certain pathogens, including Neisseria spp., and to dampen the host inflammatory response. When CEACAM1 is absent, hyperactivation of neutrophils, increased inflammatory cytokine levels, and increased mortality occur during Listeria monocytogenes infections. Until now, there has been little information regarding whether CEACAM1 function also might play a negative regulatory role in cardiovascular diseases, and no reports have appeared regarding its effects in the context of the sterile inflammation that occurs during stroke.

The article by Ludewig et al published in this issue of Circulation Research describes the first studies to assess the role of CEACAM1 in stroke outcome, with a particular focus on the effect of CEACAM1-expressing inflammatory cells in the breakdown of the BBB after focal cerebral ischemia-reperfusion. The primary findings of this elegant study were that infarct volume (as assessed by MRI), brain swelling, and BBB breakdown were all more severe in

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CEACAM1−/− mice compared with wild-type controls and were associated with a greater neurological deficit and higher poststroke mortality.

Strong evidence was obtained indicating that the augmented poststroke brain injury in CEACAM1−/− mice was mediated by a more severe inflammatory response involving an increased degree of neutrophil infiltration and release of MMP-9. The authors were able to comprehensively confirm this finding with data from immunohistochemistry, flow cytometry, and zymography studies, as well as from experiments involving stimulation of neutrophils. Showing that increased levels of MMP-9 activity could account for the entire adverse effect of CEACAM1 deletion, the authors found that neutralization of MMP-9 activity using SB-3CT in CEACAM1−/− mice returned the severity of poststroke pathology to the level seen in wild-type animals.

The potential clinical relevance of these novel findings was enhanced by the observation using immunohistochemistry that CEACAM1−MMP-9+ neutrophils were abundant in brains obtained from autopsies of stroke victims, as they were in poststroke wild-type mice. The overall conclusion by the authors was that CEACAM1 controls MMP-9 secretion by neutrophils in postischemic inflammation at the BBB after stroke, suggesting that this molecule is an important inhibitory regulator of neutrophil-mediated tissue damage and BBB breakdown after focal cerebral ischemia.

Much further work is now required to confirm and clarify the significance of these novel findings, including for patients with acute stroke. Of interest will be whether it is possible to develop a therapy designed to transiently augment neutrophil CEACAM1 activity and attenuate brain swelling after acute stroke. Moreover, it will be important to establish at what time point CEACAM1 activity is most critical, whether it is relevant for outcome after all ischemic strokes, or whether reperfusion is essential for its beneficial effects to be manifested. If reperfusion is not required, then such an anti-inflammatory therapeutic strategy might be available for many hours after the window for recombinant tissue-type plasminogen activator administration has closed.

Disclosures
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References

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