Endovascular acute ischemic stroke therapy

Applying basic science to clinical decisions

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The interface between basic science and clinical medicine is a key to an enhanced understanding of disease pathophysiology and for developing novel therapies. The term translational research is applied to this interface and provides a framework for the interaction between basic scientists and clinicians. Ischemic stroke is a medical disorder for which translational research is particularly important, because of rapidly developing advances in understanding the cellular consequences of focal brain ischemia, the contributions of the neurovascular unit to disease pathophysiology, and the role of blood vessel abnormalities. These and other factors contribute to the development and evolution of ischemic brain injury when a thrombus impairs blood flow to a brain region. Reperfusion of these ischemic brain regions with thrombolytic drugs such as tissue plasminogen activator (tPA) or by deploying a mechanical device to remove the occluding thrombus is a logical approach to ischemic stroke therapy, because each method restores the availability of oxygen and glucose-rich blood flow that potentiate salvage of ischemic tissue destined for infarction. Currently, only administration of IV tPA within 3 hours of ischemic stroke onset (likely to be extended to 4.5 hours soon) is approved by regulatory authorities, and 2 devices, the MERCI retriever and Penumbra device, have been cleared to remove a clot in the setting of acute ischemic stroke.^{1–4}

The relative paucity of available acute stroke therapies provides ample opportunity for translational researchers to interact in the endeavor to demonstrate the efficacy of additional therapies. In the past, significant barriers have existed for the rapid translation of basic science advances into clinical trials and ultimately clinical practice. The lack of adequate communication between basic and clinical researchers has been problematic, but this can be improved by joint meetings and the publication of original research articles and pertinent reviews in journals accessed by both groups. Another impediment has been the difficulty of basic researchers in securing funding to conduct translationally relevant projects.

The NIH initiative to increase funding for translational research should be helpful, as would be increasing cooperation and mutual support between academic researchers and industry. Another barrier has been the lack of animal modeling that is closely related to the clinical variables seen in stroke patients. Recent recommendations have been provided to enhance the relevance of preclinical modeling for the ultimate performance of clinical trials.⁵ Researchers interested in acute ischemic stroke from various disciplines should be aware of developments across a wide spectrum, and the promulgation of interactions among the various stakeholders is a key element for enhancing the likelihood of developing additional effective therapies.

In this Basic Science Section of the Society of Vascular and Interventional Neurology (SVIN) report, translational topics of interest to both clinicians and basic researchers are presented. Pundik and Sundararajan review current information about the mechanisms of neuronal death after focal ischemia. They discuss traditional mechanisms of cell death, the potentially deleterious consequences of reperfusion, and apoptosis, all of which are potential therapeutic targets. Khatri et al. present an overview of the blood–brain barrier (BBB) and its constituents. They also discuss the temporal effects of ischemia on the BBB and how these can lead to hemorrhagic transformation. BBB changes can be observed on MRI, as the hyperintense acute reperfusion marker. Understanding these BBB changes after focal ischemia might lead to new therapeutic targets and approaches to enhancing drug delivery. Dr. Madden provides an excellent discussion about the role of the endothelium in the development of atherosclerosis and how nitric oxide and endothelium-derived hyperpolarizing factor interact. In diabetic patients the endothelium is impaired and production of nitric oxide and reactive oxygen species is enhanced, increasing the development of atherosclerosis. Changes in the endothelium after ischemic stroke are also discussed.

In our article on imaging of the ischemic penumbra, we characterize this important ischemic region that is

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the target of acute stroke therapy and how it can be identified on several different imaging modalities. Diffusion/perfusion MRI is the most widely used imaging method for penumbral identification, and the penumbra is approximated by the region that is abnormal on perfusion MRI but normal on diffusion, the so-called perfusion/diffusion mismatch. MRI penumbral imaging has been used in several preliminary clinical trials and is providing promising information about patients more or less likely to respond to tPA when given late after stroke onset. In the article by Mehta and Nogueira, the authors present studies that characterized the composition of clots removed from stroke patients acutely after onset. The clots demonstrated several different histologic features: platelet/fibrin predominant, erythrocyte rich, and white cell predominant. The hyperdense artery sign seen on CT scanning or blooming artifact on MRI was associated with erythrocyte-predominant and mixed clot types, but not fibrin-predominant clots. Characterizing the constituents of clots may lead to an enhanced ability to lyse or remove them. In the last article, Hussain et al. provide an overview of the pharmacologic properties of antiplatelet drugs, anticoagulants, and thrombolytic drugs. This information is important for clinicians who use these agents in daily practice, so that they can have a deeper understanding of their indications and potential side effects.

The 6 articles related to pathophysiology and pharmacology cover a broad range of topics that can appropriately be labeled translational. Carefully reading and digesting their contents should provide the reader with an enhanced understanding of the material presented and provide the framework for interac-

tions between basic stroke researchers and clinical investigators.

AUTHOR CONTRIBUTIONS

M.F. participated in the writing and editing of this manuscript.

DISCLOSURE

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