Basic Science Controversy

Modeling Immunity and Inflammation in Stroke
Don't Be Afraid of Mice?
Halina Offner, Dr Med

The recent Proceedings of the National Academy of Science article by Seok et al demonstrating a poor correlation of human versus mouse genomic responses to acute inflammatory insults has unfortunately sounded an alarm in the stroke community about the use of preclinical experiments in mice to inform about inflammation in human stroke. There are significant weaknesses in the Seok’s report that detract from an easy application of its conclusions to stroke research, including relevance of the studied inflammatory conditions (trauma, burns, and endotoxemia) and disregard for age, sex, and comorbid differences in humans or mice. That being said, there remains an ongoing controversy about how best to translate inflammation information from mouse and other animal models to human stroke, especially in light of the almost universal disappointing failures in treatment approaches. The many issues involved have been expertly explored in the opinion articles below from Dr Uli Dirnagl, who discusses how preclinical stroke research in mice has predicted disease-relevant insights into human stroke, and Dr Frank Sharp, who outlines species-dependent immunologic differences that may constitute a major handicap in reliably translating results from mouse to human stroke. Although there are surely important differences of opinion, both articles agree on the need to tailor the mouse and higher animal models to best fit the human condition. In this regard, the Stroke Therapy Academic Industry Roundtable (STAIR) recommendations (modeling of age, sex, and comorbidity factors, compatibility with tissue plasminogen activator, use of biomarkers, and reproducibility of results in different laboratories) provide a necessary starting point. In addition, applicability of different models (arterial occlusion, thromboembolism, vasoconstriction, chemically induced venous thrombosis) to human stroke that is overwhelmingly ischemic should be respected. Fortunately, as noted by Uli Dirnagl below, mice are also highly sensitive to focal cerebral ischemia.

It is now well established that adaptive immunity contributes significantly to central nervous system inflammation, infarct size, and functional damage after stroke. However, a major deficiency in stroke research has been a full appreciation for age and sex differences in immune responses and outcome measures. A recent study by Furman et al reiterated the sex theme by identifying a cluster of genes involved in lipid metabolism and likely modulated by testosterone in males that accounts for significantly stronger immune responses in females. This more forceful immune response triggered by infarction and compromised during the postinfarction immunosuppressive phase (observed in both mice and humans) may explain a poorer prognosis in older females after stroke in spite of a higher incidence in males. It is readily apparent that male and female mice differ in cell death pathways due, in part, to the presence of estrogen in females that can regulate inflammatory pathways, reduce infarct volume, and provide neuroprotection. In retrospect, it is not surprising that therapies such as Tirilazad that were tested exclusively in male rodents failed in human clinical trials that included both male and female stroke subjects, with a worse functional outcome in females.

In conclusion, mouse models do provide enough similarities in their immune responses, and clinical and histological manifestations to be of value in understanding mechanisms of ischemic stroke. Clearly, however, unique genetic, biochemical and physiological differences in humans require a better understanding of the limitations of animal models. Hopefully, the continued search for immune modulators that can reduce the impact of the initial ischemic event and obviate the subsequent immune-ablation phase, with validation through use of species-independent biomarkers, will lead to successful intervention for human stroke subjects.

Sources of Funding
This work was supported by National Institutes of Health/National Institute of Neurological Disorders and Stroke grants R42 NS065515, R01 NS076013, and R01 NS075887.

Disclosures
Dr Offner and Oregon Health & Science University (OHSU) have a significant financial interest in Artielle ImmunoTherapeutics, Inc, a company that may have a commercial interest in the results of recombinant T cell receptor ligand technology used in prior publications on experimental stroke. This potential conflict of interest has been reviewed and managed by the OHSU and Veterans Affairs Medical Center Conflict of Interest in Research Committees.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association. This article is Part 3 of a 3-part article. Parts 1 and 2 appear on pages e177 and e179, respectively.

Received June 13, 2014; accepted June 26, 2014.

From the Departments of Neurology and Anesthesiology and Perioperative Medicine, Oregon Health and Science University and VA Medical Center, Portland.

Correspondence to Halina Offner, Dr Med, Neuroimmunology Research R&D-31, Veterans Affairs Medical Center, 3710 SW Veterans Hospital Rd, Portland, OR 97239. E-mail offnerva@ohsu.edu

(Stroke. 2014;45:e181-e182.)

© 2014 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.114.005642
References


Key Words: stroke ▪ treatment outcome
Modeling Immunity and Inflammation in Stroke: Don't Be Afraid of Mice?
Halina Offner

Stroke. 2014;45:e181-e182; originally published online July 24, 2014;
doi: 10.1161/STROKEAHA.114.005642
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/45/9/e181

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/