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 species such as Tirilazad that were tested exclusively in male rodent species to best fit the human condition. In this regard, the Stroke Therapy Academic Industry Roundtable (STAIR) recommendations (modeling of age, sex, and comorbid 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.

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