

## Modeling Immunity and Inflammation in Stroke: Differences Between Rodents and Humans?

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## Modeling Immunity and Inflammation in Stroke Differences Between Rodents and Humans?

Frank R. Sharp, MD; Glen C. Jickling, MD

A recent article “Genomic responses in mouse models poorly mimic human inflammatory diseases” showed that among genes that changed significantly in humans, the murine orthologs were close to random in matching their human counterparts.<sup>1</sup> Although this study focused on sepsis, it also raises questions about how well the rodent inflammatory response corresponds to the human inflammatory response after ischemic stroke.

In this essay we argue that the peripheral inflammatory response in rodent ischemic stroke models is different than in human stroke. Given the important role of the immune system in stroke, this could be a major handicap in translating results in rodent stroke models to clinical trials in patients with stroke.

Leukocyte composition in blood differs considerably in humans compared with rodents. In humans  $\approx 50\%$  to  $\approx 60\%$  of leukocytes are neutrophils and 15% to 30% are lymphocytes. In contrast, rats and mice have only 15% to 20% neutrophils and  $\approx 60\%$  lymphocytes. The impact of such a difference in stroke is uncertain, although certainly noteworthy. Functional differences in the immune systems of rodents and humans also exist. For example, rodents are much more resistant to infections compared with humans after surgical procedures. This could be important because in humans infections are associated with stroke risk and stroke outcomes. Furthermore, rodent stroke models generally involve surgery that has major effects on the immune system. Because surgery does not occur in the majority of patients with stroke, this introduces additional inflammatory differences present in rodent stroke models not present in humans.<sup>2</sup>

Differences in the peripheral immune system between humans and rodents are also reflected by differences in whole genome mRNA and microRNA expression in leukocytes. Although hundreds of genes change expression in blood after ischemic stroke in rodents and humans, only a handful of these genes were the same.<sup>2,3</sup> Similarly, although changes of many microRNA are present in the blood of rodents, only a few of these microRNA are shared with the microRNA differentially expressed in the blood of patients with ischemic stroke.<sup>4</sup> This suggests that little of the genomic immune response

that occurs in human stroke is similar to that occurring in the rodent stroke model. These stroke findings are similar to the rodent sepsis models where the blood genomic responses in rodent sepsis failed to recapitulate the genomic responses in human sepsis.<sup>1</sup>

Inflammation in stroke also differs in rodents compared with humans because of the causes of stroke and vascular risk factors. The most common rodent stroke model involves using a nylon filament to occlude an intracranial vessel. Although reproducible, this does not model the major causes of human stroke which include large vessel atherosclerosis, cardioembolism (blood clot), and small vessel lacunar disease. Most rodent stroke studies do not include atherosclerosis, thromboembolism, or small vessel disease in the models. Furthermore, the risk factors that predispose to such disease are generally not modeled including hypertension, diabetes mellitus, smoking, and hyperlipidemia. Modeling the cause of stroke and associated vascular risk factors is likely important to model the immune system in human stroke, given they profoundly affect the immune system. Large scale differences in immune cell gene expression are present between the different causes of human ischemic stroke.<sup>5</sup> Because atherosclerosis, cardioembolism, and small vessel disease are not modeled in most rodent studies, the peripheral blood inflammatory responses in the rodent models would not be expected to be similar to humans.

Given the above considerations, we propose that the immune/inflammatory molecules that are shared between rodent stroke models and human ischemic stroke may be most reasonable to study. Such molecules could initially be tested in rodent stroke models, with those showing robust effects evaluated further in primate or other animal stroke models to guide human stroke trials. In addition, it is important that rodent stroke models include atherosclerosis and thrombosis and small vessel disease and associated risk factors to better mimic the human condition.

It is not known whether rodent stroke models can predict treatments for human stroke. The hundreds of rodent stroke studies that have failed to translate to humans argue that many aspects of the rodent stroke model are not applicable to human

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stroke. Rodent clotting may be one exception because tissue-type plasminogen activator was effective in rodent and rabbit stroke clot models and did translate to a therapy that improves human ischemic stroke. However, it is not clear whether rodents are a good model of the human immune system in stroke. In fact, based on lack of success in animal sepsis models,  $\approx 150$  clinical trials have been performed evaluating agents that block inflammatory response in critically ill patients, and every one to date has failed.<sup>1</sup> Based on similar numbers of failed trials in human stroke, we suggest that the evidence indicates rodents are a poor model of the human inflammatory response, and other animal models should be used to study the inflammatory response and treatment relevant to human stroke. Notably most animals used for stroke models differ from humans in that they have a greater percentage of lymphocytes compared with neutrophils in peripheral blood including rats, mice, rabbits, sheep, macaques, baboons, and rhesus monkeys. Only dogs and cats are similar to humans in that they have a significantly greater percentage of neutrophils compared with lymphocytes in peripheral blood. Clearly, more work needs to be done to define and develop the most appropriate animal model(s) for human stroke with respect to the immune system.

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