Biology and Pathology

Central Nervous System

Animal models of stroke and relevance to human disease

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Learning Objectives:

- Understand advantages and disadvantages of commonly used models of stroke
- Know translational issues in neuroprotective research using stroke animal models
- Learn how to use small animal molecular imaging techniques to improve the bench-to-clinic translatability of basic stroke research

Dr. Box (1919 – 2003), who was a statistician and worked in the areas of quality control, time-series analysis, and design of experiments, wrote that "all models are wrong, but some are useful". The stroke community regards the failure of neuroprotective drugs in clinical trials as representing a major challenge to the doctrine that animals provide a scientifically valid model for human stroke (Macleod et al. Stroke 2004). However, the safety and effectiveness of interventions in human subjects can only be speculated from animal studies (Ioannidis. Sci Transl Med 2012). Moreover, the lack of translation between the animal work and clinical benefits does not entirely lie in the animal models, but in how we use the models and how we apply this knowledge to design of clinical trials (Willing. Stroke 2009). Another important issue is about which animal model we should use in our stroke experiments? It is determined by a series of compromises and questions we have to ask about the aims (or hypotheses) of our experiments, because no single animal model is able to encompass all of the variables known to affect human ischemic stroke (Howells et al. JCBFM 2010). We should understand the advantages and disadvantages of commonly used models of stroke (particularly those related to human relevance), which include 'intraluminal thread occlusion of the middle cerebral artery (MCA)', 'transcranial surgical occlusion of MCA', 'thromboembolic MCA occlusion', and etc. In addition to maintaining standardized and high-quality surgical performance, we should consider modeling stroke-related comorbidities such as hypertension, diabetes and hyperglycemia, hyperlipidemia, aging, and etc. We also need to keep the recommendations by the 'Stroke Therapy Academic Industry Roundtable' in mind with regards to the sample size calculation, a priori setting of inclusion and exclusion criteria, randomization, using different animal species (from rodents to gyrencephalic species), occlusion of the MCA permanently or transiently, and etc. In my talk, I will discuss the aforementioned issues and also demonstrate how small animal molecular imaging techniques could facilitate basic and translational stroke research.

Relevant Publications:

1. Park JY, Lee SU, Kim JY, Je KH, Schellingerhout D, Kim DE. A new microCT-based high-resolution blood-brain barrier imaging technique to study ischemic stroke. Stroke in press.
2. Shin IJ, Shon SM, Schellingerhout D, Park JY, Kim JY, Lee SK, Lee KD, Lee HW, Ahn BC, Kim K, Kwon IC, Kim DE. Characterization of partial ligation-induced carotid atherosclerosis model using dual-modality molecular imaging in ApoE knock-out mice. PLoS One 2013.

3. Shon SM, Choi YD, Kim JY, Lee DK, Park JY, Schellingerhout D, Kim DE. Photodynamic therapy using a protease-mediated theranostic agent reduces cathepsin-B activity in mouse atheromata in vivo. Arterioscler Thromb Vasc Biol 2013.
4. Kim DE, Kim JY, Sun IC, Schellingerhout D, Lee SK, Ahn CH, Kwon IC, Kim K. Hyperacute direct thrombus imaging using CT and gold nanoparticles. Ann Neurol 2013.
5. Chen JW, Figueiredo JL, Wojtkiewicz GR, Siegel C, Iwamoto Y, Kim DE, Nolte MW, DIckneite G, Weissleder R, Nahrendorf M. Selective factor XIIa inhibition attenuates silent brain ischemia: application of molecular imaging targeting coagulation pathway. JACC Cardiovasc Imaging 2012.
6. Kim DE, Kim JY, Nahrendorf M, Lee SK, Ryu JH, Kim K, Kwon IC, Schellingerhout D. Direct thrombus imaging as a means to control the variability of mouse embolic infarct models: the role of optical molecular imaging. Stroke 2011.

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