Target audience: Neurologist, Endocrinologist

Purpose: The objective of this study is to develop a non-invasive imaging strategy to assess the efficacy of pro-angiogenic therapy in diabetic stroke mouse model.

Methods: Ischemic stroke was induced by photothrombosis in adult male C57BL/6 and db/db mice (8-week old, n = 24). Endothelial progenitor cells (EPCs) isolated from bone marrow of C57BL/6 mice (male, 5-week old, n = 48) were intra-arterial injected into mice 24 h after surgery. The cyclic peptide (cRGDyK), Gd$^{3+}$-DTPA, IR783 and rhodamine were functionalized into the fifth generation (G5) PAMAM dendrimer to offer the αβ3 integrin-targeted nanoprobe. Control nanoprobe that has similar chemical structure but without the cyclic peptide targeting domain was also prepared. The home-made paramagnetic/optical nanoprobe 1 was intravenously injected into mice at day 10 after stroke. Magnetic resonance (MR) and near-infrared (NIR) fluorescence imaging were performed at 24 h post-injection.

Results: The signal intensity on MR and NIR imaging in ischemic-angiogenic area of db/db mice was significantly lower than in wild type mice after αβ3 integrin-targeted nanoprobe injection. After EPCs transplantation, the signal intensity was both increased in two kinds of mice compared to mice treated with saline. The enhancement of signal intensity in db/db mice was not as large as in wide type mice. Furthermore, histological analysis revealed that the microvessel density was consistent with the signal intensity from MR and NIR images.

Discussion: Pro-angiogenic therapy plays a critical role in the treatment of stroke patients with diabetes mellitus because the deficient angiogenesis after ischemia may result in worse outcomes 2. However, the efficacy of pro-angiogenic therapies is hardly to be evaluated with current diagnostic modalities. While current clinical techniques for monitoring therapeutic efficacy, such as blood flow measurements, are capable of detecting the large caliber vessels that form at the late stages of revascularization, molecular imaging with targeted contrast agents can map the early signatures of angiogenesis. The αβ3 integrin, differentially up-regulated in proliferating versus quiescent endothelial cells, is ideally suited for detection of angiogenesis 3. This study demonstrated for the first time that noninvasive imaging with targeted multi-modal nanoprobe could be utilized to detect angiogenesis in ischemic stroke. This non-invasive imaging method indicates that bone marrow derived EPCs could successfully augment the angiogenic response in wild type mice and db/db mice, although the therapeutic response was less satisfactory in db/db mice than that of wild type mice. It might be explained that partial transplanted cells were functionally impaired in diabetes 4.

Conclusion: This non-invasive imaging method shows potential for early and accurate detection of therapeutic response in diabetic stroke patients, enabling individualized optimization for a variety of treatment strategies.

References: