Advances in Stroke
Translational Medicine 2012

Anna M. Planas, PhD

Translational stroke research continues to move ahead, despite several disappointing clinical trial failures in 2012. There are several factors believed to be contributing to the difficulties in translating experimental studies to human stroke, for example, experimental stroke models might vary too significantly from human stroke, there might be biases in some experimental findings, and the pathophysiology of acute brain injury caused by stroke might be different in humans and animals. The current critical assessment of preclinical studies is driving improvement in the quality of experimental studies and expanding the number of hurdles that a molecule must overcome before proceeding to clinical research. In this short overview, we describe selected translational stroke research that has taken place in 2012.

Currently, a candidate drug for successful translation is the postsynaptic density-95 protein (PSD-95) inhibitor, Tat-NR2B9c, which uncouples postsynaptic density protein PSD-95 from neurotoxic signaling pathways.1 PSD-95 binds N-methyl-D-aspartate GluN2 subunits and the neuronal NO synthase.2 Disrupting this complex with PSD-95 inhibitor administered after stroke onset in rodents and nonhuman primate models reduced infarct volume and ameliorated the neurological deficits.1 Investigation of this therapeutic strategy has followed a process that illustrates bench-to-bed translation on the basis of the preclinical evidence, suggesting beneficial effects. Results of the Evaluating Neuroprotection in Aneurysm Coiling Therapy (ENACT) phase II trial evaluating the safety and efficacy of Tat-NR2B9c in patients with intracranial stroke after endovascular aneurysm repair showed lower stroke incidence in patients assigned to the Tat-NR2B9c group,3 but larger trials are needed to demonstrate efficacy.

Several concepts emerging from experimental findings are now being tested in humans. The notion that coadministration of an adjunctive therapy could augment the value of thrombolytic therapy is attractive but needs validation in the clinic. Several stroke trials combining hypothermia with intravenous thrombolysis are currently underway (eg, ICTuS2/3, EuroHYP-1). The benefits of hypothermia are supported by very robust results in experimental research,4 but its translation to the clinical setting is logistically challenging.5 Other ongoing trials test the hypothesis that damping oxidative stress will synergistically augment tissue plasminogen activator treatment. A phase III trial is testing the administration of the natural antioxidant, uric acid, in thrombolyzed patients because of improved outcome and smaller infarctions observed in rodents treated with this combination.6

Neurons are rapidly lost after stroke, leading to the concept time is brain.7 Accordingly, neuroprotectant therapies are more effective in animal models when they are administered shortly after stroke onset. This urgency led to the design of trials in the prehospital setting. Results of the large phase III Field Administration of Stroke Therapy - Magnesium (FAST-MAG) stroke trial, in which magnesium sulfate, a compound with antagonistic actions at the N-methyl-D-aspartate receptor, is administered in the ambulance are due to be released in the near future.

Following experimental results demonstrating anti-inflammatory actions of minocycline,8 the outcome of a phase I stroke clinical trial testing the efficacy of this drug in reducing neurological sequelae is awaited. Increasing experimental evidence supports the relationship among stroke-induced inflammation, the subsequent immune response, and outcome.9–11 The deleterious role of complement activation has been shown in experimental stroke models,12–14 and complement-induced neuronal cell death after brain ischemia can be prevented by intravenous immunoglobulin.15 Now a clinical trial (intravenous immunoglobulin/acute ischemic stroke) will test whether immunoglobulin can affect the rate of progression of brain ischemia by scavenging complement fragments. Neuroinflammation and immune responses are tightly related to abnormal function of the blood–brain barrier after brain ischemia, and the involvement of matrix metalloproteinases has been extensively documented.16,17 Loss of blood–brain barrier integrity is associated with hemorrhagic transformation, a frequent complication of thrombolysis. Therefore, strategies aimed to prevent blood–brain barrier leakage deserve future clinical investigation.

Compared with ischemic stroke, there have been less experimental investigations on intracranial hemorrhage,18 and the molecular and cellular mechanisms underlying hemorrhagic brain damage remain poorly understood.19 Secondary vasospasm after subarachnoid hemorrhage has been the main target of clinical trials, but failure of antivasospastic drugs to improve the outcome again points to the need for a better understanding of early and delayed brain injury after hemorrhage.20

Finally, cell therapy, particularly stem cell transplantation, remains an attractive future therapeutic approach.21,22 Exciting...
recent experimental findings showed that adult human somatic cells that have been reprogrammed to become induced pluripotent stem cells can form functional neurons and improve recovery after being grafted in a stroke-damaged rodent brain.23 Many clinical trials administering various types of stem cells to stroke patients are currently ongoing in China, North America, and Europe. Plasticity mechanisms supporting recovery after stroke have been demonstrated in animals after a variety of interventions,24,25 and noninvasive imaging techniques are invaluable tools to monitor some of these responses.26 However, translating restorative therapies from the laboratory to the clinic still faces tremendous challenges.25

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**Disclosures**

None.

**References**


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トランスレーショナル医療は基礎研究の成果を臨床医療につなげる橋渡し研究である。2012年には脳卒中分野でも研究が進められた。Postsynaptic density-95 protein (PSD-95) 阻害薬、Tat-NR2B9c は神経毒経路から PSD-95 を引き離し、げっ歯類やヒト以外の霊長類で脳梗塞巣を縮小し神経徴候を軽減した1。ヒトにおいても、脳動脈瘤に対する血管内治療後の医原性脳卒中患者に対して Tat-NR2B9c の神経保護効果を検討する ENACT 第 II 相試験が行われ、脳卒中頻度の低下が示された2。血栓溶解療法の効果を高める補助療法も注目されており、血栓溶解療法と低体温療法を組み合わせた臨床試験 (ICTuS2/3, EuroHYP-1) が進行中である。酸化ストレスの抑制が血栓溶解療法の効果を増強するとの仮説をもとに、抗酸化化作用を有する尿酸を血栓溶解療法時に投与する第 III 相試験が行われている。神経保護療法は、動物モデルで脳虚血後早期に施行すればより有効であるが、NMDA 受容体の阻害作用を有する硫酸マグネシウムを救急車内で投与する大規模第 III 試験の結果が待たれる。

ミノサイクリンの抗炎症作用を証明する実験により、この薬剤の効果を検討する第 I 相試験が開始された。多くの実験的エビデンスが脳卒中で誘発される炎症、免疫応答と臨床結果との関係を支持している3。補体活性化による有害作用が実験的脳卒中モデルで示されているが、脳虚血後の補体誘導性神経細胞死は、免疫グロブリン投与で防止できるため、急性期脳梗塞に対する補体誘導性静脈内投与を検討する臨床試験が行われるであろう。神経炎症、免疫応答は脳虚血後の血液脳関門の機能異常に密接に関わっており、matrix metalloproteinase の関与が広く検討されている4。血液脳関門の障害は、血栓溶解療法の出血性合併症に関連するため、血栓脳関門破綻を防ぐ戦略が将来の臨床研究の対象となる。脳虚血に比し脳出血に関する実験研究は少なく、くも膜下出血後の血管攣縮についても有効な治療薬の開発に失敗しており、出血後の早期、晚発性脳障害の病態解明が必要である。

細胞治療、特に神経幹細胞移植は、魅力的な治療アプローチである。多能性幹細胞に誘導されるようにプログラムされた成人細胞を、脳卒中損傷を受けたげっ歯類の脳に移植したところ、機能性ニューロンとなり機能回復を認められた5。脳卒中患者に様々な幹細胞を投与する臨床試験が、中国、北米、ヨーロッパで進行中である。

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