

Advancement in stroke research

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Stroke is the second most common cause of death in the world especially in the ageing population.¹ Thrombolysis and intravascular embolectomy are the main treatment and populated rapidly.^{2 3} However, the beneficiary is still limited because the mechanistic studies are behind. The basic research on stroke is improved because of new devices, novel techniques and the development of other disciplines.⁴ The update of a broad range of topics related to stroke is a widely appreciated feature. In order to improve the understanding of cellular and molecular mechanisms of stroke, the 2nd Summit of Chinese Basic Science Research on Stroke 2018 has been held in Beijing, China. Total of 60 basic stroke researchers from China and abroad attended this meeting. The meeting focused on six fields: (1) neuroprotection in acute ischaemic stroke; (2) neurorepair and regeneration; (3) neuroinflammation and neuroimmunology; (4) cognitive disorder in stroke; (5) drug/small molecule therapy for stroke; and (6) advances in optical imaging.

Although 95% of published preclinical studies on ‘neuroprotective agents’ (1990–2018) reported positive outcomes in animal models of ischaemic stroke, none translated to successful phase III trials.⁵ Studies are therefore focusing other approaches. For example, preconditioning and postconditioning induced neuroprotection are advancements in our understanding of the neurochemical basis for their neuroprotective role.⁶ Some of these studies are trying to transfer these techniques to the clinical practice. In the current issue, antioxidant agents such as hydrogen sulfide is another hot topic of neuroprotection. Numerous studies show that hydrogen sulfide impacts stroke outcomes in animal and cellular models. This action is via upregulation of the endothelium-dependent contraction and dilation function of cerebral vessels although having controversial results.⁷ In addition, Wang *et al* provided the direct evidence that nicotinamide phosphoribosyltransferase could be a promising therapeutic target for ischaemic stroke, which has been published in this issue. It is interesting that the effect and mechanism of dl-3-N-butylphthalide (NBP), a

new anti-ischaemic stroke drug developed by Chinese researchers, has been discussed by Wang *et al*.⁸ NBP could affect local blood flow and improve microcirculation during ischaemia.^{9 10} This discussion will promote and extend the use of NBP from the acute ischaemic stroke to the chronic ischaemic brain injury.

Neuroinflammation is one of the hot topics in the study of mechanism of ischaemic stroke. Microglia activation, polarisation and specific functions during the different periods of stroke have been extensively studied.¹¹ Confocal microscope or two-photon imaging techniques can now demonstrate the factors between microglial activation and ischaemia severity. In current issue, activated microglia displayed diverse polarisation phenotypes and played different functions during postischaemia repair and remodelling. Studies have found that microRNA played an important role in inflammatory response during ischaemic brain injury. Furthermore, Shen *et al* reported the relationship between non-coding RNA and neuroinflammatory response. A potential role of circRNAs in neuroinflammation and neuron functional recovery during ischaemic stroke remains unknown. Shen *et al* discussed the function of circRNAs, including circHECTD1 and circDLGAP4, in the experimental ischaemic research, which may become biomarkers and therapeutic targets for the stroke therapy.^{12 13}

In this issue, regarding the research of blood–brain barrier, Chopp’s group studied the glymphatic system using neuroimaging and immunohistochemistry techniques. Glymphatic system is a newly discovered pseudolymphatic system in the brain, which plays an important role in the removal of interstitial metabolic waste products. MRI could dynamically detect the role of glymphatic system in neurological diseases, its potential of pathways and function of modelling and so on. Further study found that diabetes mellitus and ageing could impair glymphatic system, leading to metabolic waste accumulation in the injured brain and consequently inducing cognitive dysfunction. The majority of blood–brain barrier research focuses on



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its cellular constituents while the basement membrane is less studied. In this issue, Xu *et al* focused on the role of the basement membrane in blood–brain barrier integrity, especially the major components of basement membrane including collagen IV, laminin, nidogen and perlecan, which was synthesised predominantly by brain microvascular endothelial cells, pericytes and astrocytes.

The occurrence of haemorrhagic stroke was relatively less compared with that of the ischaemic stroke. However, the mortality and morbidity of haemorrhagic stroke are higher. Mass factor, brain oedema and blood–brain barrier disruption are often studied in the haemorrhagic stroke both in experimental and clinical field; however, the results are not optimistic.¹⁴ The knowledge of postintracerebral haemorrhage neuronal death and the molecular mechanism is largely unknown. Recently, an iron-dependent form of non-apoptotic cell death known as ferroptosis has been identified. In this issue, Wan *et al* demonstrated that ferroptosis occurred after experimental haemorrhagic stroke model both in vivo and in vitro conditions and contributed to the neuronal death. They summarised that current research on iron toxicity, lipid peroxidation and ferroptosis in intracerebral haemorrhage and the underlying molecular mechanisms of ferroptosis.

Brain arteriovenous malformation (BAVM) and cerebral cavernous malformations (CCMs) often cause intracranial haemorrhage.¹⁵ Understanding the genetic abnormality and molecular mechanism of cerebral vascular diseases are extremely important. BAVM and CCMs could increase risk of haemorrhage, focal neurological defects and seizures. Studies have demonstrated that three different genes are associated with CCMs' progression, and CCM3 mutation results in a more severe form of the disease. In current issue, Wang *et al* focused on the signalling pathways mediated by CCM3 in regulating endothelial cell junction, proliferation, migration and permeability.

Cerebral small vessel disease (CSVD) was the main cause of vascular dementia. The diagnosis of CSVD is generally based on clinical symptoms or imaging features, which is controversial. In this issue, Han *et al*¹³ reviewed the current knowledge of pathological mechanisms of microvascular dysfunction and neurodegeneration in dementia and particularly focused on oxidative/nitrosative stress, cellular metabolic dysfunction, inflammatory signalling, abnormal synaptic plasticity and its implications in dementia. Advanced multimodal neuroimaging techniques such as brain network connectome analyses are currently applied to explore the underlying mechanism of vascular dementia. The knowledge of structural and functional brain network in a poststroke longitudinal

CSVD cohort was progressive, which has been published in this issue. The result showed that brain structural network disruption may play a pivot role in the cognitive decline.

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REFERENCES

1. Wang W, Jiang B, Sun H, *et al*. Prevalence, Incidence, and Mortality of Stroke in China: Results from a Nationwide Population-Based Survey of 480 687 Adults. *Circulation* 2017;135:759–71.
2. Cheng NT, Kim AS. Intravenous Thrombolysis for Acute Ischemic Stroke Within 3 Hours Versus Between 3 and 4.5 Hours of Symptom Onset. *Neurohospitalist* 2015;5:101–9.
3. Goyal M, Demchuk AM, Menon BK, *et al*. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* 2015;372:1019–30.
4. Bosetti F, Koenig JI, Ayata C, *et al*. Translational Stroke Research: Vision and Opportunities. *Stroke* 2017;48:2632–7.
5. Philip M, Benatar M, Fisher M, *et al*. Methodological quality of animal studies of neuroprotective agents currently in phase II/III acute ischemic stroke trials. *Stroke* 2009;40:577–81.
6. Li S, Hafeez A, Noorulla F, *et al*. Preconditioning in neuroprotection: From hypoxia to ischemia. *Prog Neurobiol* 2017;157:79–91.
7. Bredthauer A, Lehle K, Scheuerle A, *et al*. Intravenous hydrogen sulfide does not induce neuroprotection after aortic balloon occlusion-induced spinal cord ischemia/reperfusion injury in a human-like porcine model of ubiquitous arteriosclerosis. *Intensive Care Med Exp* 2018;6:44.
8. Wang S, Ma F, Huang L, *et al*. DI-3-n-Butylphthalide (NBP): A Promising Therapeutic Agent for Ischemic Stroke. *CNS Neurol Disord Drug Targets* 2018;17:338–47.
9. Qin C, Zhou P, Wang L, *et al*. DI-3-N-butylphthalide attenuates ischemic reperfusion injury by improving the function of cerebral artery and circulation. *J Cereb Blood Flow Metab* 2018;271678X:0271678X1877683.
10. Zhou PT, Wang LP, Qu MJ, *et al*. DI-3-N-butylphthalide promotes angiogenesis and upregulates sonic hedgehog expression after cerebral ischemia in rats. *CNS Neurosci Ther* 2019;25:748–58.
11. Ma Y, Wang J, Wang Y, *et al*. The biphasic function of microglia in ischemic stroke. *Prog Neurobiol* 2017;157:247–72.
12. Bai Y, Zhang Y, Han B, *et al*. Circular RNA DLGAP4 Ameliorates Ischemic Stroke Outcomes by Targeting miR-143 to Regulate Endothelial-Mesenchymal Transition Associated with Blood-Brain Barrier Integrity. *J Neurosci* 2018;38:32–50.
13. Han B, Zhang Y, Zhang Y, *et al*. Novel insight into circular RNA HECTD1 in astrocyte activation via autophagy by targeting MIR142-TIPARP: implications for cerebral ischemic stroke. *Autophagy* 2018;14:1164–84.
14. Xi G, Keep RF, Hoff JT. Mechanisms of brain injury after intracerebral haemorrhage. *Lancet Neurol* 2006;5:53–63.
15. Cavalcanti DD, Kalani MY, Martirosyan NL, *et al*. Cerebral cavernous malformations: from genes to proteins to disease. *J Neurosurg* 2012;116:122–32.