EDITORIAL

Special Issue on Programmed Cell Death in Stroke

Stroke occurs when the blood supply to the brain is blocked or the blood vessel ruptures. After stroke, the brain tissues die because of a lack of oxygen and glucose. Knowledge of the molecular mechanisms that underlie neuronal and nonneuronal cell death following stroke is important to allow the development of effective neuroprotective strategies. Programmed cell death (PCD), referring to apoptosis, autophagy and programmed necrosis (necroptosis and pyroptosis), plays crucial roles in the pathophysiology of stroke and has always been the research hotspot. In this special issue of *Current Neuropharmacology* on PCD in Stroke, we aimed to introduce the readers the latest advances in PCD after stroke, discuss the role of PCD in the progress of stroke pathophysiology, deciphering the potential signaling pathway, and update novel therapeutic strategies targeting PCD.

Different types of PCD (apoptosis, autophagy and necroptosis) in both hemorrhagic stroke and ischemic stroke are fully discussed in the review by Fang *et al.* Bobinger *et al.* Sekerdag *et al.* and Huang *et al.* in this issue. They provided an update on the exciting progress in PCD research, summarized the current knowledge of pathways leading to PCD after stroke, analyzed the results of animal studies and clinical trials and discussed their implications to improve the translational research. Autophagy is activated as a homeostatic mechanism and also as a stress response, therefore, it is still controversial that autophagy represents a survival or a suicide mechanism after stroke. Ho *et al.* highlighted some of the most challenging research on autophagy in subarachnoid hemorrhage, and address the potential neuropharmacological targets to prevent the early brain injury.

Interest in several important molecules (P2X7, TRAF6, IRE1, IRRK2 and Mst1) that mediate PCD in stroke has been reinforced by Zhao *et al.* Dou *et al.* Ni *et al.* Rui *et al.* and Li *et al.* respectively. P2X7 plays a crucial role in pyroptosis and necroptosis by exocytosis of lysosomes or autophagosomes; TRAF6 acts as an E3 ubiquitin ligase to induce protein ubiquitination and degradation; IRE1 senses and responds to endoplasmic reticulum stress by activating the unfolded protein response pathway; IRRK2 is closely associated with Parkinson's disease, and is a key player in apoptotic neuronal death; and Mst1 activates proteinases to magnify the apoptotic response. The detailed mechanisms about these molecules provide a comprehensive understanding of the related signaling system and offers insight into neuroprotection by targeting the pathophysiological cascades.

Stroke triggers inflammatory response as a result of cell death and the activated inflammatory cells elaborate a variety of pro-inflammatory cytokines to disrupt the blood-brain barrier (BBB) and in turn exacerbate brain damage. Inflammatory response and BBB disruption closely interact with PCD. Duris, Li and Schneider reviewed the role of inflammation and BBB broken in stroke associated PCD, and stressed that except the inhibition of PCD, controlling the inflammatory response and maintaining the integrity of BBB are also essential therapeutic strategies. Recent studies showed that Agmatine possessed the ability of anti-apoptosis and anti-inflammation in neurological diseases, and Xu *et al.* summarized the neuroprotective effects of agmatine and the underlying mechanisms in this issue. Furthermore, transcranial near-infrared laser therapy as a promising therapeutic approach, is introduced by Yao *et al.* and the possible mechanisms are discussed. It is expected that non-pharmacological interventions are important complementary and alternative therapies for stroke.

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