Regulatory Strategies for Cell Death in Neurological Diseases

This issue of CNS & Neurological Disorders - Drug Targets contains a series of articles that cover the major mechanisms of nerve injury and potential therapeutic strategies. Nerve injury mainly manifests as metabolic stress, ion disorder, biochemical, molecular and biological cascade events, eventually leading to neuronal death. Cell death is divided into two categories, Accidental Cell Death (ACD) and Regulated Cell Death (RCD); RCD includes apoptosis, necroptosis, autophagy, pyroptosis, and ferroptosis, etc. [1]. In the central nervous system, apoptosis, necroptosis, autophagy, pyroptosis, and ferroptosis are the main form of neuronal death [2, 3], which have become a potential therapeutic target for the nervous system disease [4].

Glucoma, Spinal Cord Injury (SCI), Traumatic Brain Injury (TBI), cerebral Ischemia Injury (CII), and delirium are clinical neurological diseases, resulting from a complex series of pathophysiological events, including oxidative, excitotoxicity, inflammation, and nitrative stress; such events induce neuronal death. Due to the limited understanding of their pathological mechanism, the outcomes of current clinical therapeutic approaches are not able to satisfy the need to treat these diseases. Glaucoma is a multifactorial optic neuropathy progressively characterized by structural loss of Retinal Ganglion Cells (RGCs) and irreversible loss of vision, and acute High Intraocular Pressure (aHIOP) injury-induced losses of RGCs have been explored, such as apoptosis, autophagy, and necrosis [5, 6]. Yu et al. revealed that pyroptosis plays a vital role in retinal neuronal death, especially in the ganglion cell layer, by acute HIOP injury that occurs at the 6th hour after HIOP injury. Furthermore, melatonin prevents retinal neurons of pyroptosis via NF-κB/NLRP3 axis after HIOP injury in rats [7]. SCI is a severe condition usually accompanied by an inflammatory process that give rise to uncontrolled local apoptosis and a subsequent unfavorable prognosis, and one reason for this unfavorable outcome could be the activation of the NLRP3 inflammasome [8]. He et al. demonstrated that MCC950 exerts neuroprotective effects by reducing neuronal apoptosis, preserving the survival of the remaining neurons, attenuating the severity of the damage, and promoting the recovery of motor function after SCI [9]. Perampanel is a highly selective and non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor (AMPAR) antagonist, which has been licensed as an orally administered antiepileptic drug in more than 55 countries [10]. Chen et al. found that perampanel significantly suppresses necroptosis after in vitro TBI model of primary cultured cortical neurons, as well as morphological change and inhibition of Lactate Dehydrogenase (LDH) release and caspase-3 activation [11]. Spastin participates in the growth and regeneration of neurites by severing microtubules into small segments. Li et al. showed that spastin interacts with CRMP2 to regulate neurite outgrowth and branch formation by controlling microtubule dynamics through phosphorylation modifications [12], revealing the underlying microtubule mechanism of neurites outgrowth during neuronal development and also proposing a feasible intervention pathway for reconstructing neural network connections after nerve injury.

Research on Post-Traumatic Stress Disorder (PTSD) is of great interest, especially now in the face of the global spread of COVID-19. The Long Interspersed Element-1 (LIE-1) participates in memory formation, and DNA methylation patterns of LIE-1 may suggest resilience or vulnerability factors for PTSD, of which the principal manifestation is a pathological exacerbation of fear memory [13]. Zhang et al. demonstrated that the retrotransposition of LIE-1 participates in the reconsolidation of fear memory after the reactivation of fear memory. With lamivudine treatment, spontaneous recovery decreases with time after recent and remote fear memory recall, providing clues for understanding the roles of LIE-1 in fear memory [14].

There are also three reviews that give our readers some insights and reflections. TBI is still the worldwide leading cause of mortality and morbidity in young adults. Recent insights into the TBI pathophysiology have established microglial activation as a hallmark of all types of TBI [15]. The inflammatory response to injury is necessary and beneficial, while the death of activated microglial is not. Nathalie et al. present new insights on the therapeutic and maladaptive features of the immune response after TBI with emphasis on microglial polarization, such as low-frequency electrical stimulation, IL-1R antagonism, Anakinra, anti-CD47, CSFR1 and NLRP inhibitors [16]. This review presents a guide for TBI inflammation towards neural repair and regeneration rather than secondary injury and degeneration by mitigating neuroinflammation via modulation of microglial response. In East Asia, Chinese herbal medicines have been known for centuries to protect and improve the nervous system, which have emerged as new pharmaceuticals for the treatment of ischemic neuronal injury via targeting the differently regulated cell death pathways. Wu et al. reviewed that Chinese Herbal Medicine can target death receptor-mediated and mitochondrial pathways to regulate apoptosis, necroptosis, autophagy, pyroptosis, and ferroptosis, etc. [17]. Notably, many herbs have been shown to target multiple mechanisms of regulated neuronal death and, in combination, may exert synergistic effects on signaling pathways, thereby attenuating multiple aspects of ischemic pathology. Statins, as inhibitors of 3-Hydroxy-3-Methylglutaryl Coenzyme A (HMG-CoA) reductase, have been identified as potential medications for the treatment of delirium because they can significantly reduce the incidence of delirium [18]. Chen et al. reviewed that Statins can alleviate delirium via reducing neuroinflammation, neurotransmitters, cerebral hyperperfusion, and microthrombosis, which may highlight the clinical application potential of statins in the therapy of delirium. However, the clinical effects of statins still provoke debate [19]. Thus, a larger sample size and better designed randomized trials are needed in the future, and appropriate drug or patient choice is also important.

Due to the different academic backgrounds of the researchers, each of the above studies can be regarded as an independent research area. However, these studies can be put together as a whole to provide a strong indication of the effect of drug inter-
vention on a particular neurological disorder. Therefore, given the trend and urgency in this area, we believe that this topic will attract the attention of researchers in relevant fields, including drug developers, neurobiologists and clinical neurologists. This special issue will also provide some advanced insights into the development of the field, in particular the research related to neural regeneration and functional recovery.

This issue is devoted to promote the publication of original findings and provide novel insights. Here, we have articles with scientific findings, as well as reviews, submitted by investigators at renowned medical and research institutions worldwide.

REFERENCES


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