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Stem cells and gene therapy in epilepsy management

Dito Anurogo*[1,2]
[1]International PhD Program for Cell Therapy and Regeneration Medicine (IPCTRM), College of Medicine, Taipei Medical University (TMU), Taiwan
[2]Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Makassar, South Sulawesi, Indonesia

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***Corresponding author:**
dito.anurogo@med.unismuh.ac.id

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Epilepsy is the most common nervous system disorder. About 1% of the population worldwide is thought to exhibit various types of epilepsy. Epilepsy has various risk factors. Several risk factors for epilepsy for example: stroke, cancer, traumatic brain injury, central nervous system infections, and genetic factors can influence the structure and development of the brain. Specifically, temporal lobe epilepsy (TLE) exemplifies approximately 30% of epilepsy sufferers. Characteristics of TLE are uncontrolled seizures and do not respond to antiepileptic drugs.[1,2] About 40% of TLE sufferers did not react to prevailing or medical therapy. One of the goals of epilepsy therapy is to achieve a seizure-free condition. Nevertheless, various resistance and sufferers to antiepileptic medications affect 30-40% of all epileptic sufferers. Therefore, we need a safer, more comfortable and more efficient multistrategy.

One approach in the management of epilepsy is stem cells. Stem cells are a promising strategy for the treatment of various neurodegenerative diseases (including epilepsy) in the future. One type of stem cell for epilepsy therapy is BMSCs or bone marrow stromal cells.[3,4] Bone marrow stromal cells' (BMSCs) transplantation is a inactive management of various nervous system problems. BMSCs can revitalize injured tissue and regulate the characteristics of disease hyperexcitability. The BMSC is distinguished by its self-renewal capacity and multipotence in addition to homing and replenishment characteristics.[5] The fundamental mechanisms such as: controlling inflammation, reducing neuronal degeneration and apoptosis, stimulation of neural stem cells or endogenous glia cells, and promoting self-repair mechanisms in the brain. BMSC can release a variety of trophic and cytokine factors involved in tissue repair and regeneration, has the capability to relocate to the area of injury, even across the blood-brain barrier, and reduce duration and frequency of seizures effectively.Furthermore, reduced levels of proinfamation cytokines (IL-6, IL-beta, and TNF-alpha) and elevated levels of anti-inflammatory cytokines (such as: IL-10) in serum and the brain in experimental animals, especially rats.[5–7]

Transplantation of BMSCs either via intravenous (IV) or bilateral hippocampus (IC) decreases hippocampal excitatory amino acid neurotransmitters and suppresses brain-derived neurotrophic factor mediated excitotoxicity, such as inhibition of synaptophycin immunoreactivity. The insulin-like growth factor 1 receptor (IGF-1R) activity is under-expressed. The observed improvement extends toward neurotransmitter equilibrium, where inhibitory style increases and the excitatory changes observed in mouse epilepsy models are rearranged in normal balance settings. Increased count of the number of BMSCs cells obtained through the IC route.[5,8]

The BMSC engraftment process results in an increase in the oxidative condition in the hippocampus, where there is a meaningful depression due to changes in lipid peroxide associated with an increase in antioxidant defense biomarkers, namely paraoxonase activity (PON1) and glutathione (GSH). In addition, BMSC transplantation in animal models of epilepsy results in significant downregulation of inflammatory cytokines (IL-1-beta and TNF-alpha) and apoptotic markers, caspase-3, in the hippocampus. To note, the

hippocampus is a part of the brain that plays an important role in the learning process, memory, mood regulation, resistance to depression. Hippocampal dysfunction causes comorbid behavior related to the incidence of mesial temporal lobe epilepsy (mTLE) in adults, including depression, anxiety, and memory deficits.[7,8]

Giving BMSC can open valuable insights and paradigms about the clinical advantages of stem cells as a possible choice to improve the pathological symptoms of neurodegenerative diseases, such as TLE, with neuroprotective impacts that are postulated and manifested as anti-inflammatory and anti-oxidant. In addition, PON1 activity has been shown to play an important role in neurodegeneration. BMSCs transplant promises as epilepsy therapy which still requires further research to understand its effectiveness.[5,6]

Gene therapy in the nervous system concerns the transfer and expression of genes towards tissues in the brain, especially neurons. One approach to gene therapy in epilepsy is galanin gene therapy.[9,10] Galanin is a bioactive neuropeptide, consisting of 29-30 amino acid peptides, beyond various receptors that are extensively organized in the brain. The galanin system depicts a propitious target as a localized gene therapy strategy for myriad rationales. Apart from being abundant, galanin is expressed in the brain of the temporal lobe, also in the hippocampus, where messenger RNA (mRNA) and peptide levels increase or are expounded de novo in neurons subsequently seizures. Other reasons, galanin can stifle the generalized seizures and excitatory glutamatergic transmission exogenously.[10,11] Other studies have proven that over-expression of local galanin mediated by an adeno-associated virus (AAV) vector has succeeded in suppressing generalized seizures. Overalanxation of galanin in piriformis cortex or hippocampus suppresses seizures in the intrahipocampal and intraperitoneal-induced kainate.[12] In other words, epileptogenesis induced through the ignition of the hippocampal electrically (electrical hippocampal kindling) does not appear to be affected by the overavage of galanin-mediated AAV, and only generalized (general) seizures, not focal, caused by electrical stimulation suppressed by the management. The explanation, release of galanin expressed by the virus during focal seizures, while neuronal activity is high frequency and long duration, during general seizures can release a sufficient amount of galanin transgenes to influence seizures. The addition of fibronectin release sequences to the virus vector has been shown to increase the release of constitutive galanin and suppress acute acute seizures. However, it is still unknown whether the deterrence of epileptogenesis and the constraints of focal seizures can be attained with galanin gene therapy.[2,13]

Other gene therapy scientists have developed based on the neuropeptide system that is widely expressed in the brain, neuropeptide Y (NPY) and its receptors. Endogenous NPY appears to play an important purposes in seizure regulator. Therefore, this system is propounded as a target candidate for a gene therapy paradigm in epilepsy.[14,15]

Another gene therapy is neurotrophic factors that has an important role in regulating synaptic plasticity and supporting the viability of adult cells. There are neurotrophic factors that act for protective effects in epileptogenesis, such as: brain-derived neurotrophic factor (BDNF), glial cell-line–derived neurotropic factor (GDNF), and neurotrophin-3 (NT-3). In rats models, they can postpone the development of kindling-induced generalized seizures.[16,17] The gene therapy, i.e.: GDNF, in hippocampus has no significant effects on the progress of electrical kindling epileptogenesis. Therefore, it is clearly stated the importance in establishing the neurotropic factors that have antiepileptic impacts in a gene therapy settlement.[18]

In 2004, Richichi et al used an AAV chimeric serotype vector, successfully proving that NPY transgene overexpression, encoded by NSE (neuron specific enolase) promoters, can greatly suppress epileptic status seizures induced by acute intracerebroventricular KA injection. In addition, the development of hippocampal electrical kindling is deferred and the seizure threshold is increased, indicating that NPY gene therapy can defer epileptogenesis.[19]

There have been various attempts to use CRISPR / Cas9 therapy in patients to correct causative gene defects. However, providing this technology to cross the blood-brain barrier and direct it to specific target cell types is a challenging research that is constantly being developed.[20,21] As technology advances, scientists have succeeded in modeling epilepsy in petri dishes. By harvesting human cells directly and using CRISPR/ Cas9 technology to edit the genetic code, and explain the neurobiology of various monogenic diseases, we are now entering a new era of personalized medicine where scientists can study

electrophysiological and histological changes in epilepsy patients without the need for nerve tissue humans, which can be obtained only from surgical and autopsy specimens.[22]

In the future, both in vivo mouse models and induced pluripotent stem cell (iPSC) models in vitro, are very important for our understanding of various aspects of epilepsy and other neurodevelopmental disorders. Each of these models will likely continue to contribute significantly to our understanding of epilepsy and will be a complement in the development of epilepsy management.[20,21,23,24]

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