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Induced Pluripotent Stem Cells for Stroke Treatment – A Review

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ABSTRACT
Cerebrovascular disease is the most common life-threatening neurological disorder which is characterized by the loss of neurons and glial cells in the brain. Among the neurological disorders, stroke is the most common one. Stroke therapy primarily focuses on restoring blood flow to the brain or stopping the hemorrhage in the brain which depends upon the type of the stroke. When the stem cells are injected the cells travel to the organ from which they were taken to revitalize and stimulate the organ's function and regenerate its cellular structure. Although the administration of various stem cells has shown promise in stroke models, Neural stem cells (NSCs) derived from human-induced pluripotent stem cells (IPSCS) have advantages over other cell types. In the last few years, recent development has opened new possibilities to find new cell therapies against stroke. These cells have the advantage of gaining genetic backgrounds of patients that more precisely model the disease-specific pathophysiology and phenotypes gained interest in the field of ischemic stroke therapy, due to the lack of ethical concerns and reduced risk of immune rejection. The Pluripotency of Embryonic cells has been demonstrated in vitro and in vivo and a large body of preclinical data from clinical trials have utilized exogenous approaches to stem cell therapy for stroke. In this review, we aim to summarize the recent advances in stem cell-based therapies for the treatment of stroke.

Keywords: Cell Therapy, Neural Repair, Stroke, Induced Pluripotent Stem Cells, NSC(Neural stem cells), IPSCS(human-induced pluripotent stem cells).

I. INTRODUCTION

A stroke is a neurologic deficit in which the blood supply to the brain diminishes and thus leads to a medical emergency[(1)]. It is also known as apoplexy, cerebrovascular accident, cerebral accident, and cerebral infarction[(2)]. Stroke is of two types: 1. Ischemic stroke (88%) – is when the brain's blood vessels become narrowed or blocked which leads to reduced blood flow[(3)]. Hemorrhagic stroke (12%) – is when a blood vessel in the brain leaks or ruptures[(4)]. A transient ischemic attack (TIA) also known as a mini-stroke is a temporary period(less than 24hrs) of symptoms similar to those of a stroke.

Stem cells are primal cells that retain the ability to renew themselves through cell division and can differentiate into a wide range of specialized cell types[(5)]. Scientists have recently discovered Pluripotent stem cells from Embryonic stem cells(ESCS) [(6)].These new types of cells are called induced pluripotent stem cells[(7)], [(8)] Ipscs form a class of cloned cells with characteristics similar to those of Escs and were first discovered[(9)]by Takahashi and Yamanaka using retroviruses to integrate four factors [(10)],[(11)](Sox2, Oct3/4[(12)], Klf4, c-MyC[(13)] into both mouse and adult human fibroblasts through corresponding vectors[(14), (15)]. IPSCS form a class of cloned cells with characteristics similar to those of which work by replacing damaged cells within the brain and regulating the immune system to prevent further damage to the body and brain post-stroke[(16), (17)]. The optimal time for introducing stem cells seems to be between 36 and 72 hours after diagnosing the stroke [(18)].

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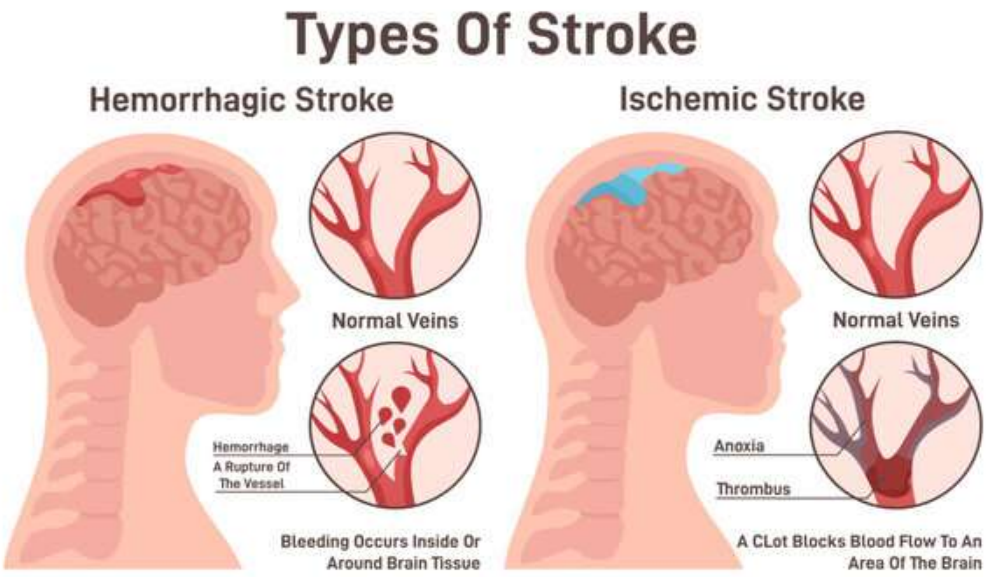

FIGURE 1: TYPES OF STROKE

Epidemiology

Nearly 800,000 people suffer from stroke each year in the United States; Almost 82-92% of these strokes are ischemic[19]. Stroke is the fifth leading cause of adult death and disability, resulting in over $72billion in annual cost. Between the tenure of 2012 to 2030, total direct medical stroke-related costs are projected to be $184billion, with the majority of the costs arising from 65 to 79 years of age[20]. Men have strokes at a younger age than women, therefore the age-adjusted incidence of stroke is 1.25times greater for men than for women. The risk of stroke for blacks is almost double that of whites, and Hispanics have a greater incidence of hemorrhagic stroke at a younger age[21]. Strokes occur in infants and children.

Etiology

In a prospective study of 27,860 women aged 45years or older who participated in the women's health study, Kurth et al found that migraine with aura was a strong risk factor common for all types of stroke[22]. The adjusted incidence of this risk factor per 1000 women per year was similar to those of other known risk factors, including systolic blood pressure 180mmHg or higher, body mass index 35 or greater, history of diabetes, family history of myocardial infarction, and smoking.

For migraine with aura, the total incidence of stroke in the study was 4.3 per 1000 women per year, the incidence of ischemic stroke was 3.4 per 1000 per year, and the incidence of hemorrhagic stroke was 0.8 per 1000 per year[23].

Anatomy of Acute Ischemic Stroke

Acute Ischemic Stroke(AIS) is characterized by the sudden loss of blood circulation to an area of the brain, typically in a vascular territory, resulting in a corresponding loss of neurologic function[24]. The brain is the most metabolically active organ in the body. While representing only 2% of the body's mass, it requires 15-20% of the total resting cardiac output to provide the necessary glucose and oxygen for its metabolism. Knowledge of cerebrovascular arterial anatomy and the territories supplied by the cerebral arteries is useful in determining which vessels are affected in acute stroke.

Pathophysiology of Acute Ischemic Stroke

The Occlusion of a cerebral blood vessel initiates a series of events that lead to irreversible neural damage and cell death in a certain part of the brain[25].In the cerebral tissue, a series of changes occur in the neurons, glial cells, and other structural components which progress from an initial function loss to a complete structural disruption and cellular death. Acute cerebral ischemia begins with the occlusion of a cerebral vessel either by a thrombus or embolus. The neurons are far more vulnerable to the effects of ischemia than the glial cells. Among these the most vulnerable are the pyramidal neurons of the hippocampus followed by neurons of the cerebellum, striatum, and neocortex. Acute ischemia stroke results from vascular occlusion secondary to thromboembolic disease[26]. Ischemia

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causes cell hypoxia and depletion of cellular adenosine triphosphate(ATP). Without ATP, there is no longer energy to maintain ionic gradients across the cell membrane and cell depolarization. The influx of sodium and calcium ions and the passive inflow of water into the cell lead to cytotoxic edema.

National Institutes of Health Stroke Scale

A useful tool for quantifying neurologic impairment is the National Institutes of Health Stroke Scale(NIHSS). The NIHSS enables the healthcare provider to rapidly determine the severity and possible location of the stroke[26]. NIHSS scores are associated with outcome and can help to identify patients who are likely to benefit from reperfusion therapies and those who are at higher risk of developing complications from the stroke itself and potential reperfusion strategies[27].

The NIHSS focuses on the following 6 major areas of neurologic examination:

Level of consciousness
Visual function
Motor function
Sensation and neglect
Cerebellar function

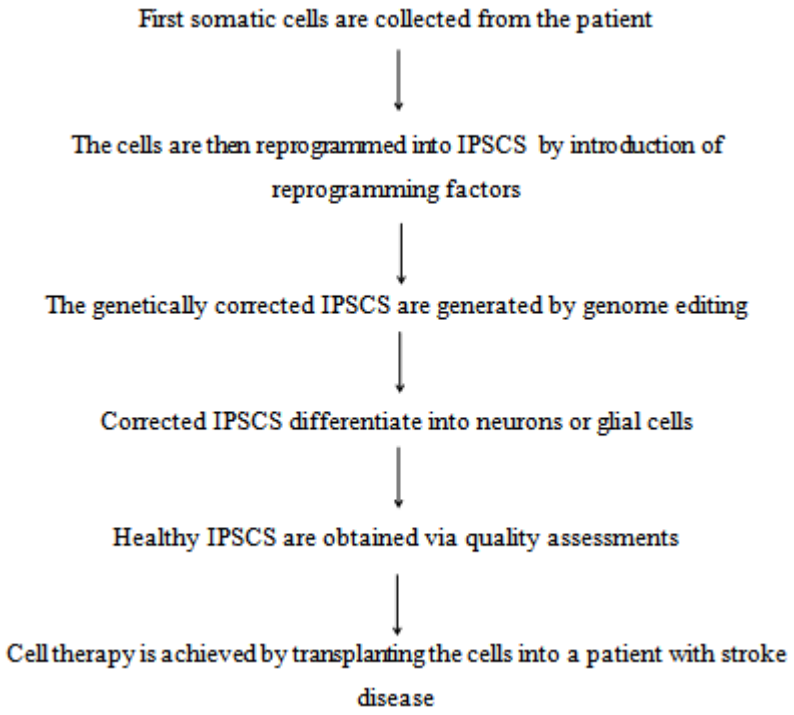
Ischemic stroke

that results from events that limit or stop blood flow, such as extracranial or intracranial thrombotic embolism, thrombosis in situ, or relative hypo-perfusion. As blood flow decreases, neurons cease functioning. Although a range of thresholds has been mentioned, irreversible neuronal ischemia and injury are believed to begin at blood flow rates of less than 18ml/100g of tissue/min, with cell death occurring rapidly at rates below 10ml/100mg of tissue/min.

Aim and Objectives

IPSCS-based cell therapy has developed rapidly and its potential has been studied for the treatment of many diseases[28]. Stem cells injected into distant arteries or veins travel to the site of a stroke in the brain to fuel the repair process.

Methodology[29],[30],[31],[32]



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Mechanism of action in stem cells

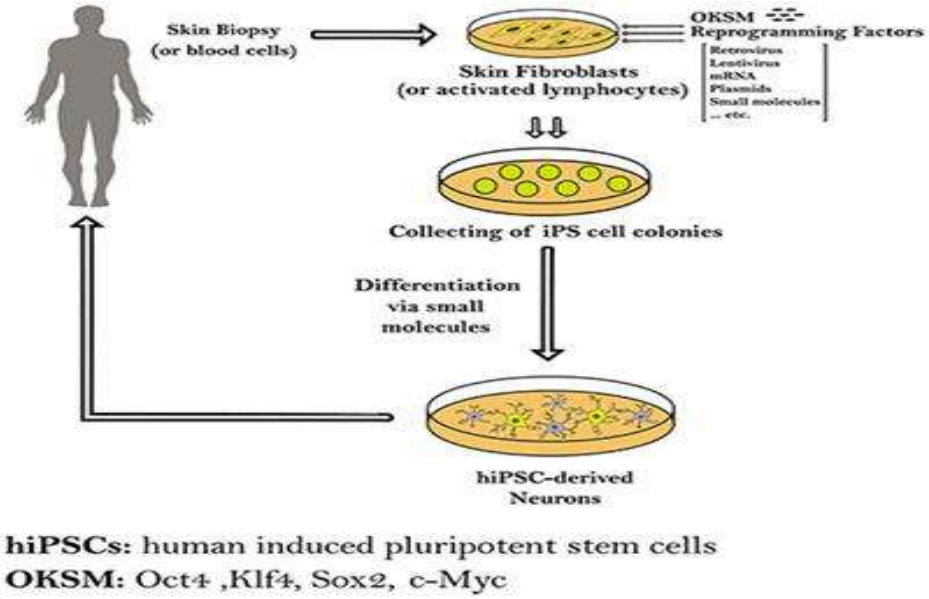

FIGURE 2: MECHANISM OF ACTION IN STEM CELLS

II. RESULTS

Stem cell transplantation of induced pluripotent stem cells is considered to be a promising alternative for ischemic stroke treatment[33]. While stem cells are still being used in clinical trials, there is evidence that combined with clot-busting and mechanical thrombectomy depicts therapy enhances the recovery of the patient. Implantation of IPSCS in animal models of ischemic stroke can effectively promote the recovery of nerve function [34], [35]. Multiple mechanisms have been proposed to account for these beneficial effects of IPSCS in treating ischemic stroke, including cell replacement, Neuroprotection, modulation of inflammatory immune responses, stimulation of angiogenesis, synaptogenesis, and endogenous neurogenesis.

III. DISCUSSION AND CONCLUSION

IPSCS that are derived from skin or blood cells have been reprogrammed back into an embryonic-like pluripotent state that enables the development of an unlimited source of any type of human cell needed for therapeutic purposes. Neurological deficit caused by ischemic stroke mainly occurs due to the loss of various nerve cells, including neurons and different types of glial cells can be created from the tissue of the same patient that will receive the transplantation, avoiding immune rejection.

Cell therapy as a treatment for stroke appears to be safe based on the data obtained in clinical trials. There is a trend towards clinical improvement in the sequelae of the patients studied, but without reaching constituent statistical significance.

The progress in stem cell biology and the creation of adult-induced pluripotent stem cells has significantly improved basic and preclinical research in disease mechanisms and generated enthusiasm for potential applications in the treatment of central nervous system(CNS) disease including "stroke". Undoubtedly stem cell-based gene therapy represents a novel potential therapeutic strategy for stroke in the future.

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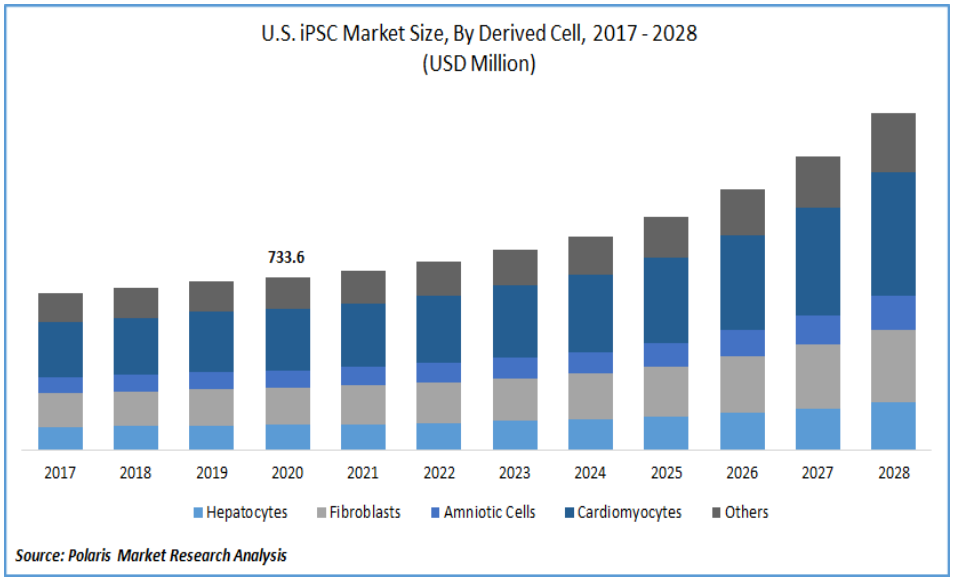

FIGURE 3: U.S. iPSC market size 2017-2018

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