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Review article

Human-induced pluripotent stem cells derived hematopoietic progenitor cells for treatment of hematopoietic failure among trauma hemorrhagic shock patients

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ABSTRACT

Hematopoietic failure (HF) has been observed in trauma hemorrhagic shock (T/HS) patients. Multiple factors are involved. Elevated serum levels of cytokines, catecholamine, granulocyte colony stimulating factor, peripheral blood hematopoietic progenitor cells (HPCs) and decreased expression of erythropoietin receptor are associated with HF among T/HS. HF leads to anaemia, susceptibility to infection, sepsis and multi-organ failure. There is a lack of molecular understanding of HF and its potential therapeutic strategies. Cell-based therapy has ability to modulate the production of inflammatory cytokines, vascular dysfunction, tissue damage and apoptosis. Human-induced pluripotent stem cells (iPSC) derived HPCs may have the ability to restore HF in T/HS. Autologous cell-based iPSC have great promises for various diseases such as Alzheimer's disease, Parkinson's disease, cardiovascular disease, diabetes, amyotrophic lateral sclerosis, and spinal cord injury without ethical concerns. Similarly, treatment with iPSC derived hematopoietic stem cells can used for the treatment of HF among T/HS and may also improve the outcome. Here, we review the potential of human iPSC derived HSC to reversed HF following T/HS.

1. Introduction

HS is a significant health issue after trauma. Mortality rate in HS patients is almost 50 percent. Hematopoietic failure is one of the facet of this response. Elevated serum cytokines (TNF-α, IL-6) levels, granulocyte colony stimulating factor (G-CSF), catecholamine, mobilization of hematopoietic progenitor cells (HPCs) from bone marrow in to peripheral blood cells and decreased expression of erythropoietin (EPO-R) receptor are also associated with HF among T/HS.[1,2] Advanced care and treatment of the traumatic injured and haemorrhage patients has undergone much progress in the last decades. Resuscitation fluid, blood and its components are used for the control of haemorrhage. However, excessive resuscitation fluid leads to immune dysfunction.[1,2] Cell-based therapy has the ability to modulate the production of inflammatory cytokines, vascular dysfunction, tissue damage and apoptosis.[3]

Human-induced pluripotent stem cells (iPSC) are emerging cells based therapy. iPSC could be used in regenerative medicine. Previous studies have reported that iPSC have a potential role in the treatment of Alzheimer's disease, Parkinson's disease, cardiovascular disease, diabetes, and amyotrophic lateral sclerosis.[4–6] Suzuki et al reported that iPSC derived HSCs have the potential to provide novel therapeutic approaches for replacing bone marrow (BM) transplantation without rejection or graft versus host disease.[7] He established unique in-vivo differentiation system firm engraftable HSCs from mouse and human iPSC in teratoma-bearing animals in combination with a maneuver to facilitate hematopoiesis. In mice, iPSC-derived HSCs migrate from teratomas into the BM and their intravenous injection into irradiated recipients resulted in multilineage and long-term reconstitution of the hematolymphopoietic system. HSCs derived from gene-corrected clonal iPSC can be used for the treatment of X-linked severe combined immunodeficiency (X-SCID) mice by using this in-vivo generation system.[7]

Currently, iPS-derived cells have been applied for sickle cell anemia, PD, hemophilia A, and acute myocardial infarction in animal models.[8] Recently, Mandai et al reported that administered of iPSC derived retinal pigment epithelial (RPE) cells were used for the treatment of age related macular degeneration (AMD) in human.[9] Recent study suggested that iPSCs-NPCs (Neuronal progenitor cells) have potential efficacy for the treatment of chronic phase of SCI.[10] Role of human-iPSC-derived HPCs has been poorly understood in T/HS patients. Our review aims at exploring the utility and feasibility of the iPSC derived HPCs for the HF among T/HS patients.

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2. Hematopoietic failure and T/HS

Suppressed hematopoietic progenitor cells has been observed in trauma injury and HS.[1,2] Recent studies shown mobilization of HPCs from BM in peripheral blood cells associated with the poor outcome in patients with T/HS.[1] Multiple factors are involved in the HF and not just the mobilization of HPCs from bone marrow in to peripheral blood. Elevated cytokines, Granulocyte colony stimulating factor (G-CSF), norepinephrine levels and decreased the expression of erythropoietin receptor (EpoR) also contributed the hematopoietic failure in T/HS Patients (Fig. 1).[1] Our previous study reported pro- and anti-inflammatory cytokines (TNF-a, IL-6, IL-10, IL 8) and MCP-1 are thought to play important roles in immune dysfunction resulting in multi-organ failure (MOF) and death. Cytokines are proteins that are important in cell signaling. It is produced by innate and adaptive immune systems. Elevated cytokines also causes HPCs apoptosis. A recent study reported that elevation of TNF-a and IL-6 were directly associated with suppression of HPCs via mitochondrial death pathways.[1]

Elevated peripheral blood HPCs is associated with the poor outcome in patients with T/HS.[11] Kumar et al reported that increased the serum levels of G-CSF associated with the mobilization of HPCs from BM in to peripheral blood.[1] T/HS-induced stress condition increased circulatory levels of norepinephrine (NE). Elevated NE levels leads to the dysregulation of CXCR4 and SDF resulting in mobilization of HPCs from BM in to peripheral blood.[1]

Our previous study observed elevated serum levels of EPO in T/HS patients when compared with control group. Elevated levels of EPO were not affected on reactivation of BM dysfunction. However, we measured the expression of BM-EpoR and found that EpoR expression was decreased in T/HS in comparison to control group. Modulation of BM-EpoR might result in HF.[1]

3. Induced pluripotent stem cells

Induced pluripotent stem cells are a kind of pluripotent stem cell that can be generated from adult cells. iPSCs assured cell-based therapy without ethical concern. iPSCs have similar properties as embryonic stem cells (ESC) and have the capability to self-renew and differentiation into any types of cells except extra-embryonic tissue such as placenta.[4–6] Yamanaka et al showed (2006) that iPSCs can be generated from adult stem cells by reprogramming. Reprogramming factors (Yamanaka factors) are the transcription factors (Oct4, Sox2, cMyc and Klf4).[12] These are pluripotency associated genes. Each gene factor is necessary to generate ESC like colonies.[12] Generation of the iPSCs is a time consuming process, 3–4 weeks for human cells and 1–2 weeks for mouse cells. The efficiency of iPSCs generation is 0.01–0.1%. In 2007, Yamanaka et al reported that generation of iPSCs from mouse fibroblast by using four retroviral mediated transcription factors (Oct4, Sox2, cMyc and Klf4). He also reported on the generation of human iPSCs from human fibroblast with factors (Oct4, Sox2, Nanog and Lin 28) using lentiviral system.[4–6,12] Recently, increased efficiency of the iPSCs by chemical agents such as (BIX-01294, valproic acid, RG108, AZA, dexamethasone, TSA, and A-83-01) (Fig. 2) has been demonstrated. Also, other cell sources, for reprogramming, have been identified (embryonic, fetal, and adult fibroblasts, neural stem cells, adipose stem cells, keratinocytes, and blood cells).[13]

4. Application of iPSCs-derived cells

4.1. iPSC-derived hematopoietic progenitor cells

Hematopoietic stem cells (HSCs) are blood cells that differentiate into the myeloid and lymphoid lineage. BM-derived stem and progenitor cells have a capacity for self-renewal, differentiation,

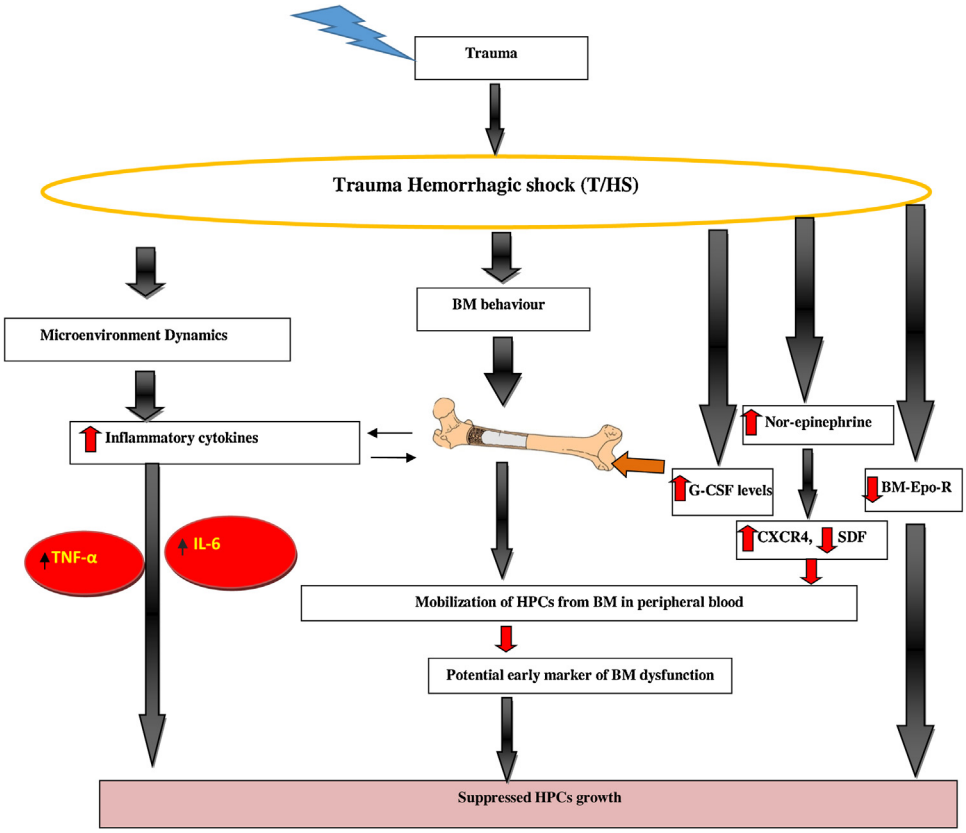

Fig. 1. Overview of suppression of Hematopoietic progenitor cells.

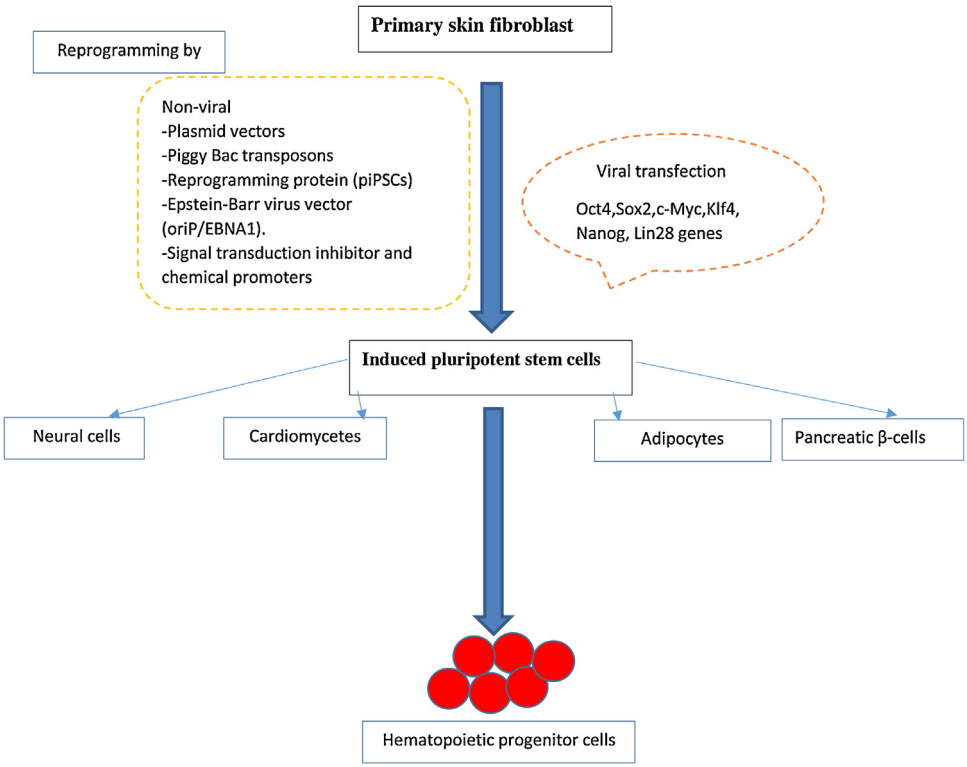

Fig. 2. Diagrammatic representation of generation of iPSC by viral and non-viral approaches.

survival, migration, and proliferation. Inappropriate strict preconditioning regimens, drug toxicity and the requirement for immunosuppression prevent routine application of these HSCs in the treatment of overwhelming hematopoietic malignancies. Previously, the significant immunologic properties of iPSC derivatives were not known to allow the determination of their potential in clinical applications.[20] Recently, iPSC-derived CD34 $^{+}$ hematopoietic progenitor cells were derived from iPSCs, which weakly express CD 80 and CD86, and highly express the T-cell inhibitory ligand PD-L1. These iPSCs-derived HPCs also induce T-cell anergy in alloreactive T cells, which can be beneficial for allogenic transplantation of iPSC-derived progenitor cells.[20] Suzuki et al proved that their teratoma-derived HPCs gave rise to adult globin gene expression in differentiated erythroid cells, one of the most absolute markers of absolute hematopoiesis (Fig. 3).[7]

4.2. iPSC-derived retinal epithelial cells

Age-related macular degeneration (AMD) is a significant cause of loss of vision. More than 10 million Americans are affected as compared to cataracts and glaucoma combined. Mendai et al decided to solve this issue by the use of iPSC derived RPE (retinal pigment epithelial) cells and designed a clinical trial. Mandai et al showed that administeration of iPSC derived RPE cells was beneficial for the treatment of AMD.[9] This was the first clinical trial (UMIN000011929) with iPSCs derived RPE for AMD patients, although only a single patients was treated. However, iPSCs derived RPE cells is the new landmark for the treatment of AMD patients. There was no serious adverse event during the follow-up.[9]

4.3. iPSC-derived neuronal progenitor cells

Treatment of SCI currently available is surgical fixation and long time rehabilitation. Methylpredisolone in high dosage have been used frequently, although with no consensus on efficacy. Until recently, there was no regenerative intervention for the treatment of SCI. Some recent studies suggested that iPSCs-NPCs (Neuronal progenitor cells) have potential efficacy for the treatment of chronic phase of SCI. Along with iPSC-NPCs transplantation, administration of chondroitinase or semaphoring 3A inhibitor helps in axonal regeneration. However, the use of iPSCs-NPCs along with rehabilitation approaches is also important to understand its clinical effectiveness.[15,16] Previous studies reported that treatment with human and murine induced pluripotent stem cell-derived neural stem/progenitor cells (iPSC-NS/PCs) promote significant recovery following transplantation into the SCI in rodents. It also enhanced the axonal regrowth and angiogenesis, and prevented the demyelination after SCI compared vehicle control animals. Tumour formation did not occur during the 12 weeks follow-up after transplantation.[15,16] Emborg et al reported that autologous transplanted iPSC-derived NPC survive for up to six months in rhesus monkey. iPSC-derived NPC differentiated in to neurons, astrocytes, and myelinating oligodendrocytes in the brains of MPTP-induced hemiparkinsonian rhesus monkey.iPSC-derived NPC also reduced the inflammatory cells and reactive glia.[17] In TBI, administeration of cell-based therapy after injury modulated inflammatory cytokines, chemokines and blood brain barrier (BBB) permeability.[18] Recently, Pepper et al reported that human iPSC-derived motor neurons may have future use in the treatment of peripheral motor nerve injury, including facial paralysis.[21]

4.4. iPSC-derived long-term neuroepithelial-like stem (hiPSC-lt-NES) cells

Animal studies have shown that treatment with hiPSC-lt-NES improved the function of stroke-injured aged brain in comparison with controls. hiPSC-lt-NES transplanted cells have increased expression of markers of neuroblasts and GABAergic neurons.[19]

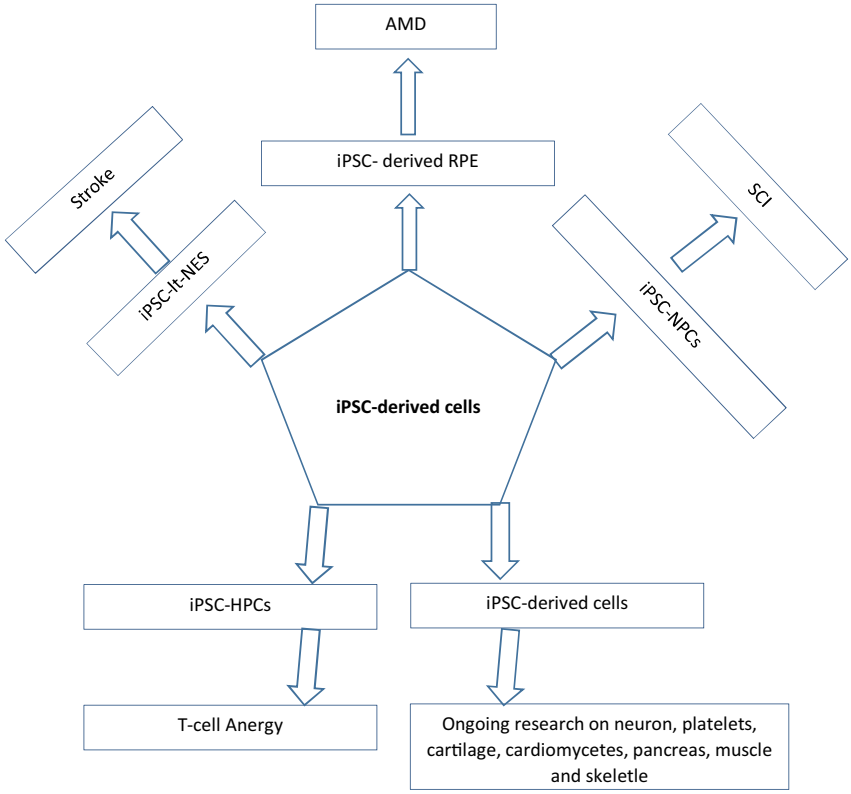

Fig. 3. Application of the iPSC-derived cells in various disease.

4.5. Ongoing clinical trial with iPSCs

There are many ongoing clinical trials with iPSCs including; Japan Agency for Medical Research and Development (AMED), iPSCs based regenerative therapy projects going on at Kyoto University (Dopamine-producing neurons, platelets, cartilage, cardiomycetes, pancreas, skeletal and muscle), Osaka University (Corneal epithelium cells, corneal endothelium cells, cardiomycetes, and hepatocytes), Keio University (Neural progenitor cells, corneal endothelium cells, and cardiomycetes), and Riken (Retinal pigment epithelium cells, photoreceptor cells, natural killer cells, teeth, hair and secretory gland). Others are, Osaka National Hospital (neural progenitor cells), Yokohama City University (liver), the University of Tokyo (liver and pancreas), Kumamoto University (liver), Chiba University (liver) and National Centre of Neurology and Psychiatry (skeletal muscle).[14]

5. Conclusion

Induced pluripotent stem cells derived HSCs may have potential benefit in the treatment of HF among T/HS. There is need for research to explored the usefulness of iPSC-derived HPCs for hematopoietic failure among T/HS.

Conflict of interest

Nil.

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