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Commentary

Breaking dogma for future therapy using stem cell - Where we have reached?

Stem cells (SCs) are functionally immature cells which have the potential to become any cell type upon stimulation. Stem cells have the unique capacity to self-renew, hence are the most promising cell source for tissue regeneration, treating cellular disorders like Parkinson's disease, to replace dead or dysfunctional cells in various traumas. Stem cells are broadly classified into embryonic stem cells (ESC), adult stem cells (ASC), based on their source and induced pluripotent stem cells (iPSC) which are genetically induced by incorporating several nuclear factors such as Sox2, c-myc, Oct4 and nanog, *etc*[1]. Pluripotent stem cells are widely used as model system to study embryonic development and cellular differentiation. Stem cells are found in many adult tissues such as epidermis, ocular, muscle, intestine, bone marrow, brain, adipose *etc*. including insulin-producing beta cells[2,3]. Growth factors and small molecules control the signals that drive these cells along the different pathways to produce mature cells from stem or progenitor cells. It is the pioneering basic research on the discovery of these signaling pathways for endoderm and pancreatic cells in early development that has paved the way for making laboratory grown beta cells[3].

A remarkable progress has been made during the past decade specifically, generating insulin producing cells. These cells represent putative beta cells, shown by expression of transcription factors known to control maturation of beta cells that secrete glucose and secretagogue-induced insulin thus restoring normal blood sugar levels after transplantation in diabetic mice[4]. Two studies[4,5] have reported generating insulin-producing cells that resemble normal beta cells from human pluripotent stem cells that share significant functional features with normal human beta cells. This provides a step forward for a potential cell therapy treatment for diabetes.

Photoreceptor loss may cause irreversible damage causing blindness in several retinal diseases. Brain- and retina-derived stem cells when transplanted into adult retina were not integrated into the outer nuclear layer and differentiated into new photoreceptors[6]. The integration of transplanted cells in the retinal region is controlled by ontogentic stage of the cell. Knowledge of the factors which define the differentiation and integration of the precursor cells in the host tissue would facilitate in identifying and enriching the cells suitable for enhancing function in the damaged region[6]. In the area of dedifferentiation of stem cells, both neural crest stem cells and mesenchymal stem cells (MSCs) from bone marrow have shown some advantage in cellular therapies to replace neurons in various neurological diseases. Neurons derived from hESCs integrate efficiently into brain circuits *in vivo*[7]. Blood vessel derived growth factors stimulate neural stem cells to differentiate neurons and this aids the brain repair itself after injury or disease, as in cases of stroke, traumatic brain injury and dementia[8]. Neuron formation is highly focused option owing to the multiple diseases includes Alzheimer's disease (AD), cerebral palsy, *etc*. Stem cells can be used as a vehicle to secrete neurotrophins, which are reduced in patients with AD. However, neuronal regeneration is very limited due to the decreased neurogenesis. Embryonic and iPSCs have been successfully used for neuron based regenerative diseases.

Recent studies have shown that MSCs from bone marrow do not migrate or differentiate in the MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine) treated striatum[9]. These factors create neuron differentiation a lucrative research option. Vierbuchen *et al*[10] have shown induction of neuronal differentiation in mouse embryonic and postnatal fibroblasts using factors *Ascl1*, *Brn2*, and *Myt1l*. Caiazzo *et al*[11], described

a way to reprogram fibroblasts from mouse and human origin into dopaminergic neurons, without going through a pluripotent stage with intact dopaminergic activity. The *in vitro* differentiation and functionality of neuron differentiation are being studied, but the *in vivo* usage and therapeutic application are way from seen[11]. The mechanism of conversion of fibroblasts into neurons is not well studied, *Mash1* gene has been shown to play a major role in the differentiation, and initiating immature neuron formation[12]. Cells of the neural crest origin have been shown to differentiate into neurons and are an easily available source compared to embryonic and mesenchymal lineage. The hair follicles have been shown to harbour pluripotent neural crest stem cells, and these can be differentiated into melanocyte, neuronal cells, adipose cells and other lineages[13].

Recent studies achieved a step forward in the development of cell-based therapies in other areas such as deafness. In one such study, cells from human embryonic and foetal stem cells identified as a candidate source have been shown to differentiate into auditory neurons that improve auditory-evoked response thresholds[14]. Similarly, pancreatic progenitor cells derived from hESCs, hold a promising new treatment for diabetes. Bone marrow mesenchymal and haematopoietic stem cells are being studied to develop better repair strategies for the osteoarticular system and blood disorders like thalassaemia. MSCs derived from human adipose tissues engineered to express suicide gene cytosine deaminase :: uracil phosphoribosyltransferase were used as vehicles to treat against gliobastoma cells[15].

In context to the current work in the issue, Kumar *et al*[16] found stem cell like cells from human skin and hair follicles were characterized for their differentiation potential into melanocytes and neurons. The study focused on the differentiation potential of stem cells from two different sources into melanocytes and neurons. It revealed the enhanced differentiation ability into melanocytes and neurons, which is very promising for the use of candidate cell type in the area of skin regeneration (melanocytes) and also neuron degenerative diseases (neuron).

Several research groups have demonstrated the versatility of embryonic stem cells, which can be differentiated into different cell types. Stem cells have the most possible therapeutic use currently in skin regeneration. The source of cells for the purpose revolves around skin graft cells and follicle cells, which are part of the neural crest, that differentiate into the different cell types of the skin, including melanocyte, keratinocyte and skin progenitor cells, *etc*. Hair follicle is a better source of stem cells for skin regeneration therapy since it has enhanced potential to differentiate into melanocyte[17]. The epidermis houses skin stem cells owing to the excessive wear and tear experienced by the organ, which help in skin repair. Skin stem cells comprise epidermal stem cells, hair follicle stem cells and melanocyte stem cells. O' Connor *et al*[18] have shown that the epidermal stem cells can be utilized to form skin grafts for the burn patients.

Future direction in this area can include better skin regeneration and that should include rapid proliferating cells with maintenance of stemness, along with regeneration of nerves. Improved culture conditions include supplementing growth factors which induce cell type specific transcription factors that can yield enhanced potential cell type to differentiate into any cell types of skin origin. The formation of neuronal cells in the skin graft might increase the sensation in the regenerated area.

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