Stem Cell Therapy for Retinopathy?

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The retina of the eye plays a dynamic function in vision and visual-perception of the external world. This occurs by phototransduction, where light or photons are translated into chemical and electrical energy [1]. These signals are transmitted to the brain through the optic nerve and any deficiency in this phenomenon could lead to impairment of the retina or loss of vision. This can occur gradually over time (chronic) or abruptly (acute) depending upon the underlying pathology. Thus, such process may lead to an irreversible impairment causing partial or complete loss of vision leading to the development of retinopathy. Types of retinopathies are Diabetic, Hypertensive, Prematurity, Radiation, Solar, Purtscher, and autoimmune retinopathy [2-8]. The primary cause of blindness in patients is Diabetic or/and Prematurity retinopathy with retinal-vascular complications. Studies have shown that such complications occur due to deprivation of appropriate cells following vascular leakage, extreme immature retinal angiogenesis, and neuronal deterioration eventually leading to loss of vision. Strategies to treat Retinopathy are ongoing but they have their own limitations and drawbacks such as laser photocoagulation (bleeding episodes requiring more laser treatments), intravitreal triamcinolone (requires intravitreal administration), and intravitreal injection of VEGF neutralizing agents such as Bevacizumab (subcapsular-cataract formation, potential for endophthalmitis) [9-11].

Stem cell (SC) therapy offers great promise for treating a terminally differentiated organ such as the eye. Different SCs such as embryonic SCs, induced pluripotent SCs, hematopoietic SCs, endothelial progenitor cells (EPC), adult mesenchymal SCs (MSC), and also the tissue specific-endogenous SCs [12-14] have been considered for the treatment. Regardless of the immense progress made in the recent years, most of the SCs studied came from animal models that did not exactly imitate human retinopathies. Moreover, specific cellular and molecular signaling mechanisms in these SCs associating to the adverse disease milieu is not thoroughly studied. 40 - 50% patients with diabetic macular edema do not respond effectively to anti-VEGF therapy suggesting that therapies targeted to VEGF-independent pathways may offer better treatment. The common anti-VEGF drugs are Bevacizumab and Ranibizumab, and there is no observation recorded for an extended time and reactivation of the disorder is always a threat [15]. However, remarkable progress in SC therapy for treating retinal disorders has been in the last few years. The source for SC for developing retinal therapies can be of two origins: 1. Endogenous (retinal), for example retinal pigment epithelial-SCs, ciliary epithelia-derived SCs [16] and Müller glia [17]. 2. Exogenous (other cell type but not from retinal origin), for example hematopoietic, MSC, embryonic, induced pluripotent, and neural SCs. It is known that retinal regeneration in adults is limited due to the intrinsic inability of retinal neurons to restart the rejuvenation and lack of its suitable milieu. In addition, many studies indicate regeneration in retinopathy predominantly done from exogenous SCs [18].

Based on the SC-therapy to address diabetic or ischemic retinopathies, when a niche cell population from bone marrow (Lin- hematopoietic-SC) was injected into the eye, it targeted activated astrocytes and aided normal angiogenesis in mice [19,20]. Endothelial cells and pericytes have a crucial role in the pathogenesis of diabetic retinopathy and harmonizing with glial cells to form a well-integrated Blood-Retinal Barrier [21]. With this notion, majority of the studies had a goal to recuperate such cell types and achieve a normal physiological balance. In a study, vascular progenitors derived from embryonic-SC or cord blood derived-induced pluripotent-SC were able to migrate, integrate, and repair retinal vasculature in a retinal ischemia reperfusion injury model [13]. Various adult-SC of non-retinal origin can be considered for developing therapies for traumatic and degenerative eye disease including glaucoma and AMD. A Neurotropic factor, progranulin produced by Adipose derived-SC have shown to be neuroprotective in the light-induced retinal-damage model [22]. MSC from
umbilical cord blood are known to differentiate into functional EPC [23] and exhibit pericyte-like phenotype [24]. SCs derived from the Wharton's jelly of fetal umbilical cord have the capacity to differentiate into retinal progenitor cells [25]. These SCs secrete immunomodulatory and neurotropic factors such as BDNF, TGFβ1, NT-3 and transplanting such SCs will contribute toward neural repair [26]. Lastly, by injecting a niche-pluripotent SC population (from peripheral blood mononuclear cells) into the sub-retinal space, SCs migrated into the damaged tissue and differentiated into respective cells types expressing human photo-receptor specific marker, Rhodopsin [27,28] thus showing the true potential of the SC therapy.

**Remarks**

However, unintended SC differentiation upon transplantation is likely to affect the function and efficacy of the treatment and most importantly the safety aspect. Hence, before proceeding to the clinical trials, extensive investigation (long-term studies relevant to humans) has to done to improve the SCs processing, induction, differentiation, and transplantation. Yet, challenges in testing and validation remains, whilst translating cell therapies from preclinical studies into the human clinic studies.

**Bibliography**

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