

# Novel cell-based therapies for diabetic retinopathy



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### 1. Introduction

Diabetic retinopathy (DR), a common complication of diabetes mellitus, is the major cause of blindness in the middle-aged and elderly populations, affecting approximately 20% of diabetic patients [1]. The retina is a hyper metabolically active tissue that demands a dynamic interaction of cells ranging from light-sensing photoreceptors to neurons transferring electrochemical signals to the brain via glia and vascular tissue. The function of neurons is dependent on the complex interdependence of retinal cells, which includes the formation of a blood-retinal barrier (BRB). Diabetes has a negative impact on this dynamic system because it alters normal cell-cell interactions, resulting in profound vascular abnormalities, blood-barrier loss, and impaired neuronal function. The lifetime risk of developing DR in type 2 diabetes mellitus (T2DM) patients is 50-60% compared to 90% in type 1 diabetes mellitus patients (T1DM) [2].

### 2. Pathophysiology of DR

#### 2.1 Inflammation, Oxidative stress, and Metabolism

Hyperglycemia is an important contributor to the development of diabetes mellitus. The hexosamine pathway, advanced glycation end products accumulation, polyol pathway, protein kinase C pathway, and polymerase activation are all identified as underlying mechanisms as to how elevated blood glucose leads to DR. These pathways cause metabolic dysfunctions, which lead to additional insults and progression of DR [3]. The pathophysiological demonstration of DR is caused by metabolic dysregulations, oxidative imbalance, and inflammatory imbalance.

#### 2.2 Cellular degeneration

The early loss of retinal function and peripheral nerve involvement in DR patients cannot be explained solely by micro vasculopathy. Hence, further exploratory research in this regard suggests that retinal ganglion cells and amacrine cells are the first neurons to undergo apoptosis and that the apoptotic rate of photoreceptors is also increased. Since vascular and neural impairments are both present in DR pathology, the concept of the neurovascular unit (NVU) was proposed to combine all of the above theories [5]. Autoregulation serves one of the most significant physiological roles of the NVU in maintaining normal visual function by

matching changes in metabolic activity with changes in retinal blood flow. Such a phenomenon is found to be impaired in asymptomatic early-stage DR patients, implying that NVU dysregulation may be central to DR pathogenesis [6].

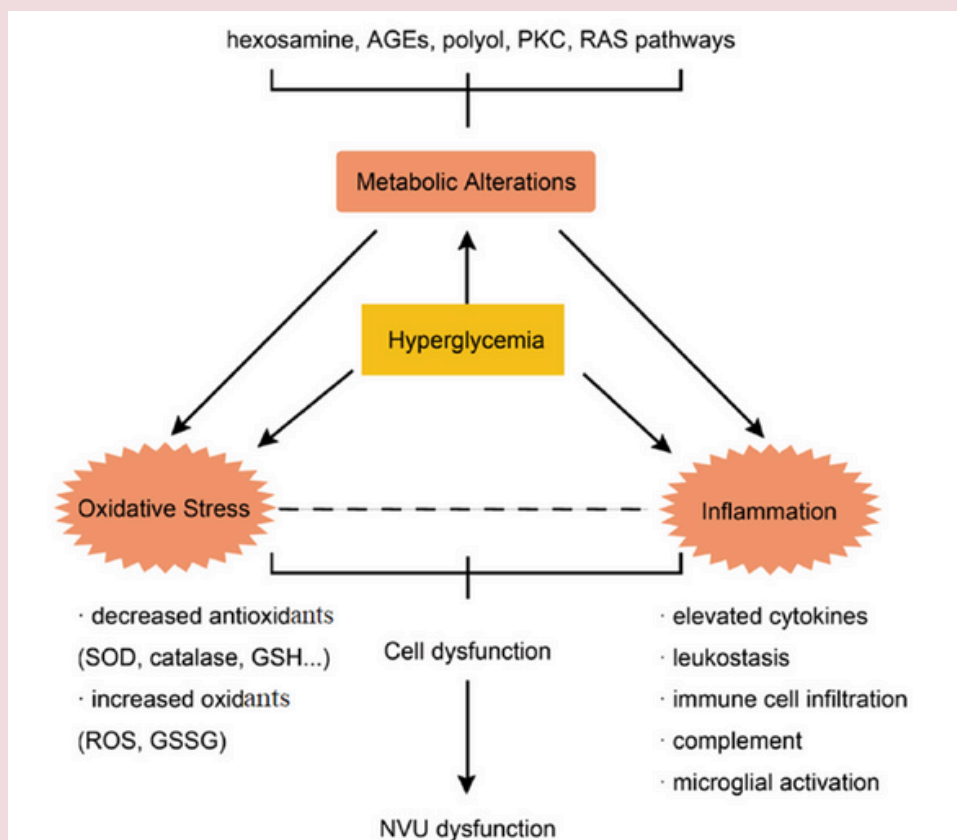


Figure 1: Metabolic dysregulation, inflammation and oxidative stress-based pathophysiology of DR [4]

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## 3. Need for cell-based therapies

Processes involved in the pathogenesis of DR such as metabolic dysregulation, oxidative stress, and inflammation alter the neurovascular functions of the retina. DR interventions now include preventive strategies and interventions such as corticosteroids, anti-vascular endothelial growth factor (VEGF) agents, laser photocoagulation, surgeries, and so on. However, these strategies rarely reverse the diabetic retina's radial pathological changes, let alone the side effects of invasive surgeries and recurring injections, resulting in a poor long-term prognosis of

DR. As a result, novel treatments, primarily based on cellular and genetic interventions, with the goal of achieving long-term and effective disease reversal are being researched, providing new hope for DR treatment [4].

#### **4. Various cell-based therapies utilized in DR**

Various cells such as Endothelial Progenitor Cells (EPCs), Pluripotent Stem Cells (PSCs), Embryonic Stem Cells (ESCs), Induced Pluripotent Stem cells (iPSCs), Human Mesenchymal Stem Cells (MSCs) have been utilized in cell-based therapies for vascular regeneration owing to their peculiar characteristics.

##### *4.1 Endothelial Progenitor Cells*

Endothelial progenitor cells (EPCs) are circulating cells that are thought to play a crucial role in tissue regeneration by boosting blood vessel repair and assisting in the reperfusion of ischemic areas [7]. Asahara et al., 1997 pioneered the use of adult stem cells to regenerate blood vessels. Postnatal neovascularization was thought to be solely based on fully differentiated Endothelial Cells (ECs) derived from pre-existing blood vessels. Asahara, on the other hand, demonstrated that putative hematopoietic precursor cells (CD34+, Flk-1+/KDR+) from human adult circulating blood cells can differentiate to ECs in vitro and termed them "endothelial progenitor cells (EPCs)" [8]. These cells are more resistant to oxidative stress than other differentiated and mature endothelial cells. The elimination of retinal ischemia caused by diabetic retinopathy is likely to be part of a successful therapeutic method utilizing these cells in the treatment of DR [9].

##### *4.2 Pluripotent & Induced Pluripotent Stem Cells*

From day 5-7 of the embryo, stem cells can be obtained from blastocysts before implantation. Pluripotent cells are capable of differentiating into any type of mature cell. In recent years, reprogramming techniques have made it possible to create stem cells from somatic cells as well; these cells are known as induced pluripotent stem cells [10]. iPSC technology enables the generation of patient-specific cells, avoiding some of the ethical concerns associated with ESCs, allograft rejection, and immunogenicity, which also allows scale-up production of the desired cell lineage, generating new prospects for regenerative medicine [11]. Using hematopoietic progenitor cells generated from iPSC in vitro, researchers were able to restore multiple lineages in irradiated genetically identical adult recipient mice [12]. Damage to the tight junctions of the retinal pigment epithelium in diabetic animal models can destroy the retinal pigment epithelium barrier, indicating that cell replacement therapies using retinal pigment epithelium cells may be important for the treatment of diabetic retinopathy [13].

##### *4.3 Embryonic Stem Cells*

ESCs are deduced from the inner cell mass of blastocyst-stage embryos and have the capacity to self-renew and differentiate into all adult cell types derived from the three embryonic germ layers. Researchers found that transplanting human ESC (hESC)-derived retinal cells into the subretinal space of adult mice promoted the differentiation of hESC-derived retinal cells into functional photoreceptors and improved light responses in these mice [14]. Despite the potential benefits of ESC in retinal replacement therapies, ethical and immune rejection concerns still need to be taken into consideration.

#### 4.4 Human Mesenchymal Stem Cells

Human adult MSCs, found in a wide range of tissues including bone marrow and adipose tissue, are a type of adult multipotent stem cell with a more limited differentiation potential and self-renewal ability. These cells have been utilized in neuro-retinal degenerative diseases such as DR owing to their ability to secrete neuroprotective growth factors such as basic fibroblast growth factor (bFGF) and ciliary neurotrophic factor (CNTF). When injected locally or systemically, both bone marrow and adipose-derived MSCs have been shown to differentiate into photoreceptors and retinal pigment epithelium in disease models [15,16]. In vivo studies have been conducted to further investigate the potential of EC-derived MSCs, which have been shown to improve muscular angiogenesis and blood perfusion restoration in a mouse hindlimb ischemia model [17].

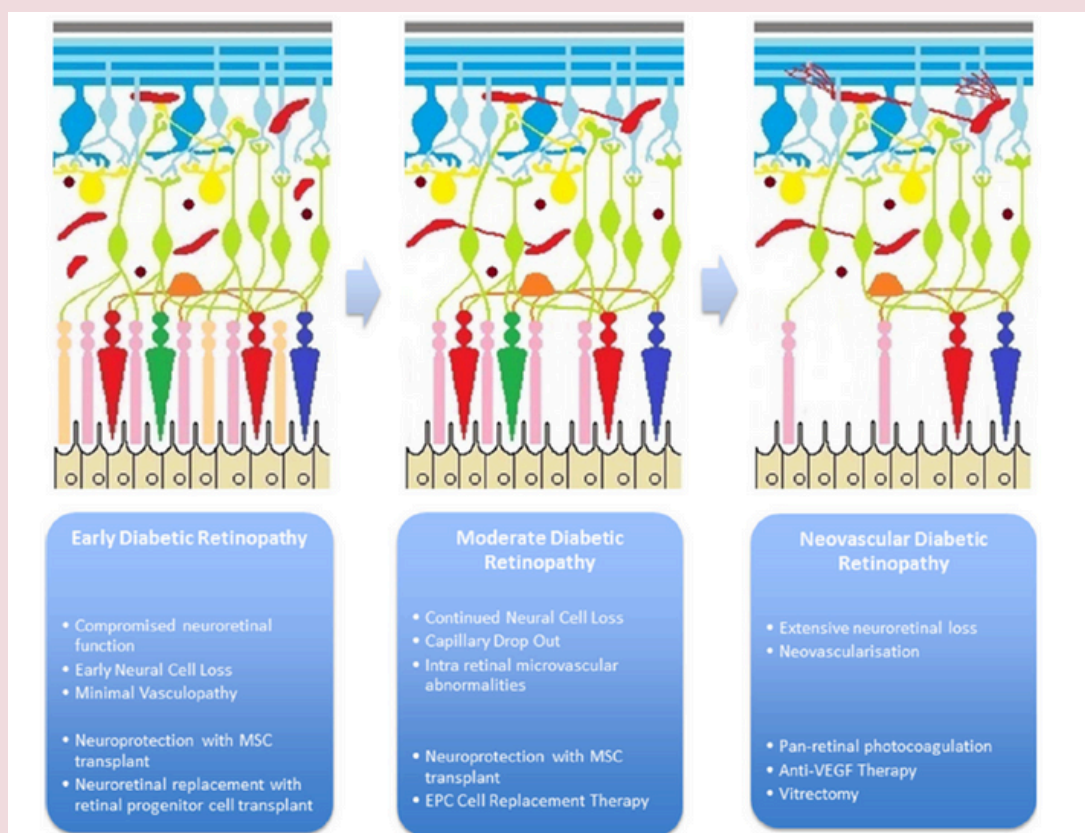


Figure 2: Use of stem cells derived at different stages of DR. Providing MSC-derived neuroprotection and neuroretinal cell replacement early in the course of the disease may be beneficial. EPC-derived vascular regeneration may be beneficial even in the advanced stages of the disease [18].

## 5. Conclusion

In contrast to the current end-stage approaches to diabetic retinopathy, cell-based therapy may offer an exciting new approach. In order to improve vascular repair, reverse ischemia, lessen hypoxic/inflammatory stimuli, and stop the progression of these diseases to their late, sight-threatening stages, this strategy is intended to target early/intermediate stages of vaso-degeneration. However, there remain some drawbacks to be looked after such as allograft rejection, immunogenicity, and production scale-up issues along with their inefficiency in the later stage of the disease.

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