Inherited Retinal Degenerations

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In this issue of IrJO Movassat et al (P: 33-38) present a case series of leber's congenital amaurosis (LCA). LCA is the most severe form of inherited retinal dystrophy responsible for congenital blindness with an early age of onset and accounts for at least 5% of all inherited retinal diseases which affect about one in 3500 individuals in the world.

Usually degenerative anomalies of the retina initially affect the rods which cause night-blindness and regression of the visual fields, but progressively the cones, retinal vessels and other cells get involved in this degenerative process.

In the past decade many efforts have been focused on the genetics and pathogenesis of these blinding diseases.

Although, more than 100 genes have been discovered for these degenerative diseases, we are at the beginning of a long road.

Gene therapy has been used successfully to stop or slow down the degeneration of photoreceptors in species presenting degenerative diseases similar to human. Gene therapy has been used in mice, rodents, dogs and some primates.

The RPE65\(^{-/-}\) dogs present a naturally occurring and rapidly blinding disease similar to human LCA. A recombinant adeno-associated virus (AAV) carrying RPE65 injected into the vitreous has delayed the progression of the degeneration, which has been shown by successive ERG's.\(^2\)

Since nucleic acids are not capable to penetrate cell membranes they are inserted into the viruses to deliver the normal genes to the photoreceptors replacing the mutated genes. Adenoviruses, AAV, and Lentiviruses have been used for this purpose.

This rescuing process is possible only when at least some photoreceptors are functional; and when apoptosis is extensive and most cells have been degenerated or highly affected, as it is the case in most of our retinitis pigmentosa (RP) patients, gene therapy would not be effective.

In another field of research in these degenerative diseases stem cells have been used successfully to treat retinal degenerative disease, but a functional vasculature of the retina is necessary to maintain the survival of the implanted cells.

In two mouse models of retinal degeneration rd1, and rd10, resembling human leber amaurosis, when a fraction of mouse or human adults bone marrow stem cells (Lineage-Negative hematopoietic stem cells [Lin\(^{-}\)HSCs]) containing endothelial precursor cells injected into the eye of neonatal mouse, not only the sensory cells were replaced but also the retinal vessels were rescued, and active, functional photoreceptors were preserved.\(^3\)

Stem cells have been isolated and cultured from many sources such as embryonic tissues, adult bone and even the retina but in human have shown little ability to differentiate into retinal phenotype.\(^4\) Transplantation of stem cells and restoration of visual function in human is possible but only when the donor cells are at a specific stage of development which is a precursor-photorceptor stage.
This very complex procedure is controlled by genetic and extrinsic regulatory factors and needs a genetic switch to activate, control and complete the procedure. This very complex pathway has not yet been completely understood and applied in molecular research.

Every day, new discoveries and technology are being applied in the molecular research fields which give us hope to treat and cure these degenerative retinal diseases in a near future.

References