UPDATE ON RETINAL TRANSPLANTATION AND ITS CLINICAL LIMITATIONS

TRASPLANTES RETINIANOS: ESTADO ACTUAL Y SUS PROBLEMAS EN LA APLICACIÓN CLÍNICA

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At present, cellular and genetic therapies constitute realistic approaches for the treatment of neurodegenerative retina diseases.

Developments in genetic science have provided a new vision of the physiology and pathogenesis of specific genetically-induced retinal diseases and potential treatments thereof through the modification of the genes involved. Although considerable progress has been made in treatments on animal models (as well as in clinical experimentation phases) for some pathologies such as Leber’s congenital amaurosis, gene therapy doesn’t appear to be an option in patients with important visual loss derived from loss of photoreceptors or retinal pigmentary epithelium cells (RPE) which have caused large-scale changes in retinal circuits (1,2).

The use of said treatments is also difficult in pathologies comprising a large amount of ethiopathogenic factors, such as Age-Related Macular Degeneration, with the additional drawback of its high cost in diseases where researchers continue to discover a vast amount of genes involved in the pathogeny thereof, for instance Pigmentary Retinosis.

The possibility of re-establishing eyesight was the purpose of initial research into retinal transplantations performed at the brain level, which proved that the transplant had the capacity of axonal growth and establishment of synapses and physiological responses (3).

In the light of said results, it was easy to think that if the transplantation was made at the sub-retinal level, the cells involved would be able to establish new synaptic connections and develop functional capacities.

There are two different approaches to retinal transplantations: the first is based on limiting the loss of photoreceptors by introducing cells to maintain their function, and the second option is replacing the photoreceptors which have been lost. Both options share some problems, like selecting the right type of cells, the transplantation method (isolated cells or full tissue), how to minimize postop inflammatory reactions and immune responses, selecting the method for performing the transplantation, the optimization of its efficiency and postop success assessment.

The selection of the type of cell will depend on the cause of photoreceptor loss. If the disease originated in RPE defects, this type of cell or others can be injected to improve the chemical environment at the sub-retinal space. The range of cells utilized for this purpose include RPE cells, iris pigmented cells or immortalized cells, improving cell survival as well as achieving the preservation of its functions (4,5).

For improving the cellular environment, growth factors or neurotrophines have been injected, growth factor-secreting cells (such as Schwann cells) have been transplanted, neurotrophic factor-releasing encapsulated cells have been injected in the vitreous, as well as transplants of rods, which can produce growth factors improving the survival of the rods.

If the defect is primarily in the photoreceptors, retinal elements or films can be introduced. These strategies must take into account the vast synaptic reorganization which takes place upon neuronal death (1,2). Therefore, their usefulness is restricted to very early degenerative stages.

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The two main questions which arise after said treatments are: can eyesight be actually maintained after the transplantation? and, how do the injected cells perform? Functional and visual capacity tests have been made on rodents utilizing behavior tests, electroretinograms, light adaptation curves, response levels in the superior colliculum, pupil reflex test, among others, suggesting that function is maintained.

The way in which the cells function after a transplant is not clear. It has been suggested that injected RPE cells or photoreceptors take over the functions of defective cells, but there is very little literature capable of identifying the transplanted cells, and even less demonstrating the phagocytosis capacity of the injected RPE. Possibly they improve the performance of existing cells.

Even though the first retinal transplant was carried out 60 years ago, it was only in the eighties that it attracted a great deal of attention. The first results in animals caused a surge of enthusiasm. However, many questions remain to be answered. The first transplants in humans were made in the nineties and served to verify their safety but failed to show spectacular functional results.

The likely cause for the lack of function is that the transplantations are made in very advanced cases of retinal degeneration, when the changes in secondary neurons are so important that there is no possibility of establishing synaptic transmission after the large-scale reshaping of the retinal circuits.

At present, the majority of groups which perform transplants are convinced that more basic research is needed for a deeper knowledge of transplants and their results in the improvement of the donor cells’ environment, the chemical manipulation of Bruch’s membrane to enable the RPE cells to attach to it, the design of improved strategies for replacing lost photoreceptors by modulating the immune response or aiding the re-establishment of neuronal circuits, and for ways to minimize inflammatory and immune responses, among many other topics.

Finally, an additional therapeutic option should be considered: the injection of multi-potential stem cells with the capacity of aiding cellular survival as well as replacing lost photoreceptors. Recently, ES human embryo stem cells have been used, or bone marrow stem cells which, injected in the subretinal space or the vitreous, have exhibited the ability of differentiating themselves into neurons and integrating into the retinal circuits. These results give rise to great expectations for treating retinal pathologies, although increased basic research is still needed to determine the mechanisms involved in said differentiation, integration and functionality of transplanted cells.

In summary, a great deal of progress has taken place in the field of retinal transplants throughout the last two decades. It is necessary to be aware of this progress and of other therapeutic options such as the utilization of neurotrophins or stem cells, or of visual prosthetic systems, in order to find answers to patients’ questions and inform them so they can have realistic expectations, including the existing limitations as well as the ongoing research being carried out in this field.

REFERENCES


