

Degeneration of Rods and Cones in Retinitis Pigmentosa

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Abstract

Retinitis Pigmentosa, most commonly characterized by night blindness and loss of peripheral vision, is a rare genetically inherited group of diseases affecting the retina of the eye. It is estimated that 1 in 4000 people in the USA are affected by some form of the disease. Retinitis Pigmentosa (RP), is caused by a mutation or change in one or more of 55 genes. There are many causes to this disease as RP presents with many different symptoms and biological effects on the eye. These are then grouped together because they share a common result, deterioration of vision. Presently, there is no cure for the disease. Most of the present therapies are aimed at preserving visual function and preventing or slowing further cell death. Restoring vision is particularly difficult because human photoreceptors are not produced and do not divide after birth and therefore their loss is irreversible. Experimentation in gene and stem cell transplantation to retard the advance of the disease, as well as drug therapies and surgeries to diminish the effects of the disease are ongoing and have found some limited success.

List of Acronyms:

RP: Retinitis Pigmentosa

RGCs: Retinal ganglion cells

NGF: Nerve growth factor

IPS: Induced pluripotent stem

DHA: Docosahexaenoic acid

Introduction

The eyeball consists of three main layers and is one of the most complex organs in the body (fig.1). The outermost layer, the fibrous tunic, is made up of the sclera and the cornea. Then the middle layer, the vascular layer, consists of the ciliary body, iris and choroid. The innermost layer is the nervous tunic which consists of the retina. The retina contains two types of photo-

receptor cells, the rods and cones. Near the beginning stage it is hard to detect the disease, especially if there is no familial history, as most daily functions are not affected. The slow regressive pattern of deterioration that defines RP presents in the onset of the disease with night blindness and the reduction of peripheral vision. The lack of peripheral vision in the day becomes apparent when incidents like not seeing pedestrians walking, not noticing cars approaching from the side while driving, or missing handshakes when greeting people occur. As the disease advances patients become sensitive to light. This often leads to reading difficulties and difficulty perceiving pale colors particularly in the blue and yellow tones.

In the last stages as the cones begin to be more affected the vision field continues to narrow, and the light sensitivity continues to grow. Often patients are still able to read a little, usually with a magnifying glass, until the central visual field vanishes. Usually patients can still perceive light.

Methods

Articles and studies researched in this paper were obtained through the EBSCO and ProQuest databases with access provided by the Touro College Library. Images and diagrams that are used throughout the paper were obtained from the research articles cited.

How is RP Inherited?

RP is a progressive inherited disease that occurs in one of three ways: autosomal recessive inheritance, autosomal dominant inheritance, or X-linked inheritance. Autosomal recessive inheritance happens when both the mother and father are carriers of the recessive gene mutation giving them a 1 in 4 chances of having a child with the disorder. The parents typically do not show any signs or symptoms of the disease. Autosomal dominant inheritance happens when one parent has a dominant gene mutation giving them a 1 in 2 chance of having a child with the disorder. In this form of the disease there is often a parent and other members of the family with the disease.

X-linked inheritance is when the mutated gene is on one of the X-chromosomes. It can be passed on to sons who inherit only one X-chromosome and cannot offset the gene with their Y-chromosome. Sons from mothers that are X-linked carriers

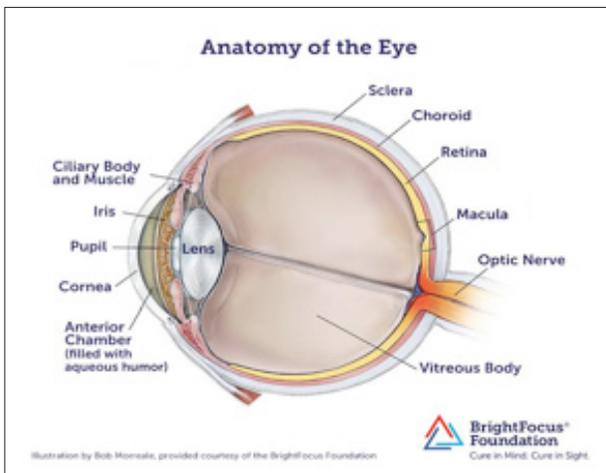


Fig 1

receptor cells, the rods and cones. The rods and cones absorb and convert light into electrical signals that are then sent to the brain. The rod and cone cells are present throughout the retina with the exception of the fovea, the center of the retina, where only cone cells are present. Rod cells are accountable for peripheral and night vision whereas cone cells are accountable for more direct visual functions like reading, driving and facial recognition. The rods allow us to see in dim light and the cones allow us to see color and details.

RP can manifest itself as early as the first years of life,

have a 1 in 2 chances of having the disease. Fathers with X-linked RP cannot pass the disease on to their sons. Girls inheriting only 1 affected X-chromosome have a 1 in 2 chance of being carriers. Girls usually need both X-chromosomes affected to get the disease. There are a small minority of woman who get the disease with only one X-chromosome affected. X-linked inheritance is by and large thought to be the most severe form of RP and can begin in early childhood (Melamud, 2006).

In a situation where only one person in the family is affected, the disease is referred to as simplex. These cases could be the result of small families where there are few possible relatives to be affected, or it could be the result of a new gene mutation.

RP is primarily a monogenic inherited disease. This form of inheritance refers to a single gene controlling a genetic trait. Digenic inheritance refers to a disease that is inherited through the mutation of two interacting genes. There are many diseases caused by single gene mutations but so far very few have been found which are caused by mutations in at least one copy of two genes interacting. Digenic inheritance is a rare form of the genetically complex RP.

How are the Rods and Cones Damaged?

RP is caused by the loss of use of the rods and cones. It is typified by the initial loss of rod function followed by the death of the cones. It is the genetic mutation that causes the initial rod death, but the subsequent cone death is thought to be caused by its dependence on the rods. It is the loss of the cones that causes the severe blindness associated with the disease.

The rhodopsin genes' function is to encode a protein called rhodopsin in the rod cells. Rhodopsin absorbs the light that is then converted into electrical signals in the rods. The most common cause of autosomal dominant RP is a sequence variation in the rhodopsin gene (Schuster, 2005).

Mutations in the rhodopsin genes obstruct their ability to function properly and are the cause of over 25%, of autosomal-dominant RP cases. The alteration at a specific point accounts for the difference in the disease expression within families. The majority of the mutations affect the folding, and stability of the rhodopsin molecule (Terry, et. al. 2017). In other forms of the disease the mutations produce a protein that is toxic to the cell, or the mutation doesn't allow the cell to function properly. As a result, the rods followed by the cones cease to function and slow progressive vision loss occurs (Jensen, 2016).

Discussion

While there is a great deal of research on the genetic sources of the disease, there is still much to be discovered and studied to extend our knowledge and treat RP effectively. For example, most of the current research focuses on the etiology of RP. However, because of the many differing genetic mutations that cause RP there is very little research that can be done on the

disease as a whole, but it is rather approached in a very specific type by type manner. Since most of the accepted approaches target specific versions of the disease, they are only beneficial to particular groups of patients.

In the past few years there has been a vast amount of scientific research into treatments for RP. These include surgical, pharmacological and non-invasive treatments.

Recent studies have shown that as the rods degenerate, the cones are deprived of glucose and eventually die. The photoreceptors are dependent on glucose in order to function properly. One of the symptoms of RP is the breakdown of this process.

Muller cells, which are non-neural cells of the retina, serve to protect the retina by providing a conduit to transport glucose to the photoreceptors, remove debris and provide electrical and mechanical support of the neural retina. The Muller cells are among the first to show signs of metabolic changes in the retinal degeneration of RP and are among the last cells left in the degenerate retina. As RP progresses, the Muller cells follow a chaotic metabolic path. Unlike the precise cohesive response Muller cells exhibit in healthy retinas, they appear to react to the degenerating photoreceptors in an unfamiliar non-homogeneous manner. The remodeling of the retinal cells caused by cell stress and death is an unavoidable consequence of the progression of the disease (Pfeiffer, et. al. 2016).

As the photoreceptors degenerate, the surviving rods and cones reorganize (fig. 2). This is followed by the adjustment of inner retinal components such as the neurons, the glial cells and the blood vessels. This process of remodeling cannot be explained as an attempt to produce new cells as retinal cells cannot be reproduced or regrown. It is rather seen as a reaction to one or more possible negative inputs that causes the remodeling and the eventual cell death. The course of the photoreceptor cell death is dependent of the underlying genetic mutation, the type of RP. The path of the inner retinal layer degeneration is

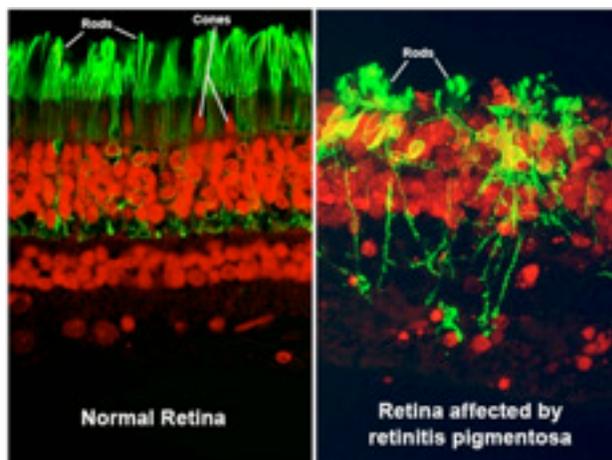


Fig. 2 Normal retina vs. reorganization of the retina in a patient with RP (Raw.com)

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similar in spite of the differing underlying genetic mutation. This is significant in the search for a cure or a reversal of at least part of the progressive path of the disease.

The complex biological process of retinal remodeling is an active field of retinal investigation, as it shows promise for therapeutic treatments of the disease (Terray, et. al. 2017).

Scientists have tried a number of ways to surgically reverse this process. One of the methods is that they have attempted to bypass the ineffective rods by surgically replacing them and restoring the transportation of glucose to the cones. The cones remain latent for a period of time before they die and if the glucose supply can be replenished before that time they can be regenerated. In a study of rod transplantation, the rods from healthy mice were transplanted into RP affected mice that were totally lacking rods but still had some functioning cones. These mice were compared to a control group of RP mice to measure the normal degeneration for the same period of time. Two weeks after surgery the number of functioning cones were compared between the two groups of mice. Those mice that received transplanted healthy rods showed 40% greater cone survival than untreated mice. Another surgical method that has shown potential as a treatment for RP is the placement of glucose directly under the retina so as to regenerate and reactivate the cones (Mohand-Said, 2000).

The objective of the rod transplantation surgery is to help the survival of the cones as they gradually deteriorate over time and ultimately to prevent blindness from occurring. This is different than other surgical treatments being tried, such as cataract surgery. In cataract surgery the lens of the eye is removed and replaced because the lens has become cloudy and thus the person's vision is cloudy. For RP patients with progressively limiting vision the start of cataracts can advance the loss of vision significantly. Therefore, cataract surgery has been found to be beneficial in some cases of RP. The difference between the rod replacement surgery attempts and cataract surgery is their goals. While they both are trying to restore as much sight as possible, the rod replacement surgery is trying to stop the progression of the disease by replacing the genetically affected rods. By contrast the cataract surgery is treating only the symptoms and not the underlying cause (Dikopf, et. al. 2013).

There are also a vast number of non-surgical research studies being done. One of the first symptoms of RP is night blindness and difficulties with dark adaptation. Researchers have investigated the use of antipsychotic drugs on RP given that the side effect of certain specific drugs of this type is increased light sensitivity. The increase in light sensitivity produced by these drugs was compared to their known adverse side effects to determine if they could be a useful treatment in RP.

Most antipsychotic drugs act as dopamine antagonists. They block the dopamine receptors. In order to reach the photoreceptors, incoming light must first pass through all the cell layers

of the retina. The first layer is composed of the ganglion cells. The ganglion cells are a type of neuron in the inner surface of the retina that transmit information to the brain. Between the photoreceptor and the ganglion cells there are bipolar cells that transmit signals from the photoreceptor to the ganglion cell. The ganglion cell receptive fields are subdivided into two parts, center and surround. They operate in an ON center OFF surround or an OFF center ON surround manner. In the ON center/OFF surround a small ray of light in the center increases the cells response. An Off center On surround has the opposite effect where a small ray of light in the center inhibits the cells response.

The antipsychotic drugs haloperidol and clozapine were tested to see whether they could similarly alter the light responses of the retinal ganglion cells (RGCs) in the rat retinas.

The drugs have the effect of transforming abnormal long latent ON-center RGCs into Off-center cells. It is believed that these RGCs might have been Off-center cells early in the onset of the disease. Antipsychotic drugs are divided into two categories, typical and atypical. The difference between these two categories is the side effects they produce. Atypical antipsychotic drugs like clozapine are considered second generation antipsychotic drugs that have fewer negative side effects than the first-generation drugs like haloperidol. The responses of the retinas of the rats were recorded before and after the application of the various drugs. Both haloperidol and clozapine increased light sensitivity of the affected rat retinas. For those retinas that exhibited an abnormally long latency ON response to the onset of a small spot of light, both haloperidol and clozapine brought about a change and a reduction in the long latency ON response. Both these drugs act as an antagonist to receptors in the rats. The haloperidol acts as a D2 receptor antagonist while the clozapine acts on the D2 receptor as well as a 5-HT2A (serotonin) receptor antagonist. On the whole, the results imply that antipsychotic drugs may be useful in temporarily improving vision in patients with RP (Jensen, 2016).

Other pharmacological treatments such as the supplementation of different vitamins, DHA (docosahexaenoic acid) a type of omega 3 fatty acid, oral valproic acid and topical brimonidine tartrate NGF drops, are all being explored in the hope they can help to protect and slow the progression of the disease.

Vitamin A is a powerful antioxidant that has been found to be essential for good vision, eye health and the ability to help protect the eyes from night blindness and age-related degeneration. Supplementation of vitamin A over a period of 4 to 6 years showed a significantly slower rate of visual decline. The study included different genetic types of RP as well as children in the early stages of the disease. These results contrasted the results of the supplementation of vitamin E. Patients receiving vitamin E showed a greater loss of retinal function than placebo groups.

In a 4-year study of DHA supplementation vs. placebo the loss rate of cone and rod function was not appreciably different.

Another study comparing the effects of taking DHA with vitamin A or taking vitamin with a placebo showed that the addition of the DHA did not alter the results of the effects of the vitamin A on RP patients. The rate of decline of the progression of the disease remained the same (Sacchetti, 2015).

Nerve Growth Factor

NGF, nerve growth factor, is important in the regulation, growth and survival of the neurons. It has been found to promote the recovery of neuronal damage in several animals. NGF drops were administered in a 10-day trial to see the short-term effect of the drops on patients with advanced stages of RP. The possible adverse effect of the drops was monitored closely. The study showed neither adverse effects nor significant improvement in RP patients.

Stem Cell

Stem cell transplantation is a potential treatment that is showing great promise. Allogeneic stem cell transplantation, which are stem cells taken from matching donors, or human embryos, have the potential to be effective and safe. However, there is the ongoing controversial debate on the morality of using embryonic tissue in medical experiments or treatments. This issue coupled with the greater risk of rejection and need for immunosuppressant therapy when using allogeneic stem cells has encouraged scientists to investigate the use of autologous stem cells transplantations, which are treatments using stem cells derived from the patients themselves (Bassuk, et. al. 2016).

IPS: Induced Pluripotent Stem Cells

IPS cells, induced pluripotent stem cells are autologous stem cells that come from the person's own skin or blood cells. These cells are then reprogrammed to enable them to develop into any type of human cell.

The use of IPS cells as a treatment for RP has shown some promise in restoring some of the lost vision. Because of the many different genetic causes of RP there is hope of developing specific IPS cells to target precisely the various forms of the disease independently. The goal of this treatment is to edit and correct the patient's pathogenic mutation in very specific type by type RP cases. X-linked RP is a very aggressive form of the disease. IPS cells have been used in studies to try to correct the specific X-linked form of the disease and have been found to correct 13% of the gene mutation that causes the X-linked RP. Researchers are optimistic with their success of the gene editing treatment of X-linked RP thus far. It establishes that this treatment should be continued to be studied and used as part of autologous transplantation of other photoreceptor degeneration cases.

There are still other challenges with this treatment due to complications with incorrect placement, the development of

tumors and disturbance of other types of cell which need to be resolved in order to further the use of this stem cells research (Bassuk, et.al. 2016).

In contrast to the pharmaceutical approach to the early onset of light sensitivity and vision loss, the nonpharmacological interventions are based on strategies of light protection. The use of specialized electronic glasses to protect the eye from contact with light has been employed. In more advanced stages of RP there is the Argus II which combines both glasses with surgery. The Argus II involves the implantation of an artificial device that must connect to a functioning optic nerve. Electrodes are then implanted into the eye and connected to the glasses that can convert images into electrical pulses that the brain perceives as patterns of light.

Conclusion

There is promising research for treating the symptoms of RP. There is also promising research into fixing the underlying genetic mutation that is associated with RP, with the use of stem cell therapy. Continued research is needed before the stem cell therapy can be used as a widespread treatment. It is the goal of researchers to treat patients earlier on in the progression of the disease, before complete visual function is lost.

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