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Retinal transplantation—advantages of intact fetal sheets

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Abstract

Retinal transplantation aims to prevent blindness and to restore eyesight, i.e., to rescue photoreceptors or to replace damaged photoreceptors with the hope of reestablishing neural circuitry. Retinal donor tissue has been transplanted as dissociated cells or intact sheets. A promising experimental paradigm is the subretinal transplantation of sheets of fetal retina with or without its attached retinal pigment epithelium (RPE) into recipient rats with retinal degeneration. As long as healthy RPE either from the host or from the graft is present, such transplants can develop lamination resembling a normal retina. Different methods have been used to demonstrate transplant/host connectivity. In two different rat retinal degeneration models, visually evoked responses can be demonstrated in an area of the superior colliculus corresponding to the placement of the transplant in the retina. In summary, sheets of fetal retina can morphologically repair an area of a degenerated retina, and there is evidence to suggest that transplants form synaptic connections with the host and restore visual responses in blind rats.

CONTENTS

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1. Introduction

Retinal transplantation was introduced in the 1980s with high expectations. As these expectations could not be fulfilled in a short time, interest waned and funding has been sporadic. It was not realized by many that this difficult research takes time to be successful. As shown in this review, many encouraging results have been obtained that have increased the possibility that this research might help people with retinal diseases.

In many retinal degenerations, photoreceptors and/or retinal pigment epithelium (RPE) degenerate even though the neural retina that connects to the brain can still remain relatively intact (Eisenfeld et al., 1984; Santos et al., 1997; Humayun et al., 1999) (for review, see Papermaster and Windle, 1995; Milam et al., 1998).

There are two transplantation approaches: (1) transplantation of RPE (Gouras et al., 1984; Gouras et al., 1985; Li and Turner, 1988; Lopez et al., 1989; Sheedlo et al., 1989; LaVail et al., 1992a; Algvere et al., 1994; Little et al., 1996; Castillo et al., 1997; Little et al., 1998; Lund et al., 1998; Algvere et al., 1999), iris pigment epithelium (Rezai et al., 1997; Schraermeyer et al., 1999) and Schwann cells (Lawrence et al., 2000) *to rescue existing photoreceptors* in a degenerating retina and (2) transplantation of tissue containing the missing or dysfunctional cells *to replace lost cells* (Silverman and Hughes, 1989a; Del Cerro et al., 1991; Silverman et al., 1992; Gouras et al., 1993, 1994; Seiler and Aramant, 1998; Aramant et al., 1999; Kwan et al., 1999; Aramant and Seiler, 2000a). The success of the first approach, apart from replacing dysfunctional RPE cells, is in large part based on the delivery of trophic factors by transplanted cells because similar effects can be achieved by delivery of trophic factors to the eye (Faktorovich et al., 1990; LaVail et al., 1992b; Unoki et al., 1994; Masuda et al., 1995; Perry et al., 1995; Reh et al., 1996; Cayouette and Gravel, 1997; LaVail et al., 1998; Chong et al., 1999). Most studies over the last 10–15 years have dealt with the transplantation of RPE.

This review is focused on the second approach of replacing lost cells. The hypothesis is: if the diseased photoreceptors can be replaced and the new cells can make appropriate connections with the still functional part of the retina, a degenerated retina might be repaired and eyesight improved. Of course, the benefit of additional trophic effects of such transplants on the host retina cannot be excluded.

Many retinal diseases affect both photoreceptors and RPE, and need replacement of both cell types. However, most reviews and meetings have neglected to consider and discuss this possibility. One group has developed a unique approach: transplantation of sheets of fetal retina together with its RPE (Aramant et al., 1999). This will be discussed in Section 5.

1.1. Early development of retinal transplantation

In 1959, Royo and Quay reported the successful transplantation of fetal eyes to the anterior chamber of the maternal eye in rats (Royo and Quay, 1959). This experiment was taken up again in 1985 when strips and cell aggregates of fetal retina were injected into the anterior chamber of rats of the same and of different strains (Del Cerro et al., 1985). Retina was first transplanted to the retina in 1986 (Turner and Blair,

1986). This model was initially based on transplanting neonatal retinal cell aggregates to a retinal lesion site of a normal rat retina, and later extended to include embryonic retina (Aramant et al., 1988, 1990a; Aramant and Seiler, 1991). Around this time, several other groups started transplanting retinal cells to retina: dissociated retinal cells (Del Cerro et al., 1988, 1989, 1991), retinal microaggregates (i.e., $<0.2\,mm^2$ pieces) (Gouras et al., 1993, 1994; Ivert et al., 1998) or photoreceptor sheets (Silverman and Hughes, 1989a; Silverman et al., 1992) to animal models of retinal degeneration.

2. Retinal degeneration models used for transplantation

To test experimentally whether retinal transplants could be beneficial to damaged retina, different models of photoreceptor degeneration have been used.

2.1. Light damage

The light damage models used by Silverman and Del Cerro were obtained by exposing albino rats to constant white light for 2–4 weeks at 1900 lx (Silverman and Hughes, 1989b) or 4–5 weeks at 3000–3500 lx (Del Cerro, 1990; Del Cerro et al., 1991) with the light coming from the top of the cage. Although it was claimed that this light exposure specifically only damages the photoreceptors, such an exposure will inevitably also affect the RPE cells, as can be seen in Del Cerro et al. (1995).

A light damage model was developed by Seiler et al. (2000) in which albino SD rats are exposed to blue light (680–1290 lx) surrounding the cage. This leads to an even destruction of photoreceptors after only 2–4 days of exposure while keeping the RPE intact. The outer nuclear layer (normally 8–10 rows) was reduced to one row of cells in the central retina and to 2–3 rows in the periphery, in both the superior and the inferior retina. Apoptotic nuclei appeared exclusively in the photoreceptor layer after 1–5 days exposure to blue light. Using behavioral methods, visual thresholds of some rats were determined before exposure and remeasured between 18 and 52 days after exposure. Visual performance in the behavioral test was substantially impaired. Average ERG a- and b-wave amplitudes of light-damaged rats were both reduced by about 98%.

This light damage model was used for the first experiments with fetal intact-sheet transplants (Seiler and Aramant, 1998; Seiler et al., 1999b) (Fig. 1).

Although a relatively even light damage could be achieved with this light damage model, it was not possible to completely eliminate the photoreceptors in the retinal periphery.

2.2. Inherited models of retinal degeneration used for transplantation

2.2.1. RCS rat

The Royal College of Surgeons (RCS) rat is a well-established model of RPE dysfunction with subsequent photoreceptor degeneration (Mullen and LaVail, 1976; D'Cruz et al., 2000). RCS RPE cells cannot phagocytose rod outer segments; the accumulating debris in the subretinal space leads to photoreceptor death. Prior to complete photoreceptor degeneration, at the age of 3–4 weeks, photoreceptors can be rescued by transplantation of RPE (Li and Turner, 1988; Lopez et al., 1989; Li et al., 1990). Sham surgery has a transient rescue effect (Silverman and Hughes, 1990). This is probably due to the upregulation of trophic factors, e.g., RCS rat photoreceptors can also be rescued by bFGF treatment (Faktorovich et al., 1990). The photoreceptor rescue can also be demonstrated by electrophysiological (Yamamoto et al., 1993; Jiang and Hamasaki, 1994; Sauvé et al., 1998) and behavioral tests (Little et al., 1998). Although IPE transplants can rescue photoreceptors, their effect is not different from sham surgery (Schraermeyer et al., 1999). Transplantation of Schwann cells that produce many trophic factors and do not phagocytose outer segments can also rescue RCS photoreceptor cells (Lawrence et al., 2000). This indicates that photoreceptor death in the RCS rat is also due to lack of trophic factors. The sham surgery effect on promoting photoreceptor recovery and survival is an interesting observation and obviously complicates the analysis of the transplantation results.

Gouras has transplanted adult photoreceptors to 3–4 month old RCS rats (Gouras et al., 1991a, b). The results are described in Section 3.1.

Aramant et al. (1999) have transplanted sheets of fetal retina together with its RPE into RCS rats at an age (1.3–2.1 months) when transplanted RPE cells no longer rescue photoreceptor cells (Figs. 2A–C, Fig. 3) and shown that such transplants can restore visual responses in this rat with a degenerated retina (Woch et al., 2001) (Fig. 5). Although there was a sham surgery effect, responses in sham surgery rats were significantly different from those of transplanted rats.

The initial results indicated that only sheets of retina cografted with its RPE into RCS rats would develop normal photoreceptor morphology. However, recently, fetal retina transplanted without RPE has been seen to develop well-organized transplants at 5–7 months after transplantation. These transplants exhibited 5 rows of photoreceptors with inner and outer segments (Fig. 2D). It may be that the transplant photoreceptors do not have such a high metabolic activity as in normal retina so that the RCS RPE can handle the outer segments of the transplants. In addition, many microglial cells were observed in the subretinal space that can also digest

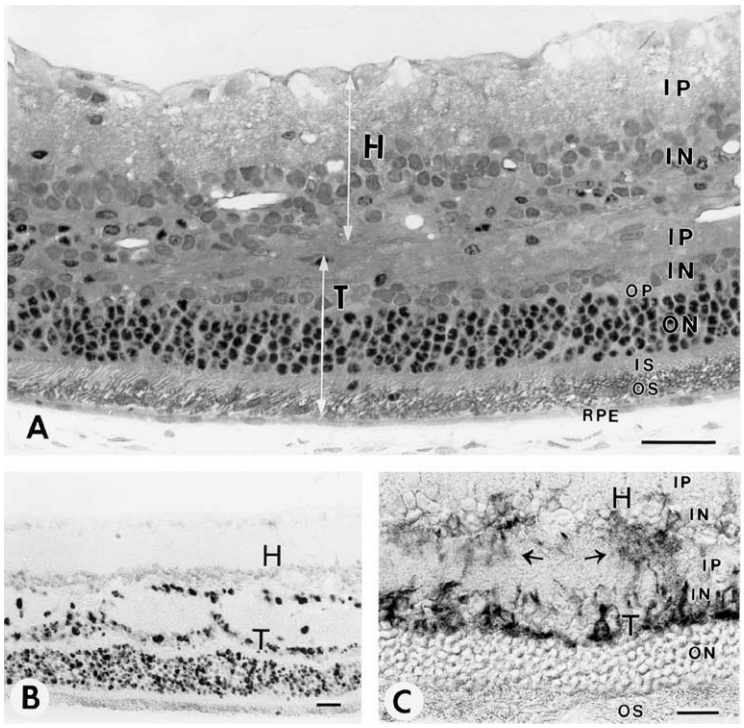

Fig. 1. Repaired damaged retina. (A) A sheet-transplant has morphologically reconstructed an area of a light-damaged retina, not like a normal, but resembling a normal retina. The transplant has developed 6–8 rows of photoreceptors and all retinal layers, although the inner retinal layers are less well developed. Note the good integration with the host retina. An inner nuclear layer is seen in both the host and the transplant. Microglia can be seen in the subretinal space. E19 retinal transplant, 1.8 months after transplantation to light-damaged Sprague Dawley host. (B) Donor cells labeled with bromo-deoxy-uridine (BrdU), prelabeled at E16/17. E19 retinal transplant to light-damaged rat, 2 months after transplantation. (C) Rod bipolar cells in host and transplant. Note the processes in the interface between transplant and host (arrows). PKC immunostaining. E17 transplant to light-damaged rat, 4.9 months after transplantation. Bars = 20 μm. (Legends: H = host; T = transplant; IP = inner plexiform layer; IN = inner nuclear layer; ON = outer nuclear layer; RPE = retinal pigment epithelium; IS = inner segments; OS = outer segments; B, Bruch's = Bruch's membrane.)

outer segments (Fig. 2D) analogous to the microglia/macrophages digesting outer segments previously observed inside rosettes of aggregate transplants (Aramant and Seiler, 1994; Larsson et al., 1999). This intriguing observation needs further investigation.

2.2.2. *rd mouse*

The rd mouse, a naturally occurring model of human retinitis pigmentosa, has a defect in the β-phosphodiesterase gene (Bowes et al., 1990). It is a fast model of retinal degeneration; the photoreceptors start to degenerate at postnatal day 11 before outer segments can form (Blanks et al., 1974; Carter-Dawson et al., 1978; Bowes et al., 1988; Kuo et al., 1989). Since the retina does not have any rods left at the age of 3 weeks, transplanted photoreceptors are easily identifiable. The rd mouse has been used both for microaggregate retinal transplants (Gouras et al., 1992, 1994; Radner et al., 2001), transplantation of mechanically dissociated retinal cells (Kwan et al., 1999) (Section 3.1), and for transplantation of photoreceptor sheets (Mohand-Said et al., 1997) (Section 3.2). The rd mouse has the disadvantage of rapid retinal degeneration so the transplantation has to be done at a very early age to see an effect (Kwan et al., 1999; Radner et al., 2001).

2.2.3. *Transgenic rodent models of retinal degeneration*

There are many transgenic mouse models of retinal degeneration available which have not yet been used for transplantation. They have been used in different attempts to rescue photoreceptors by trophic factors and gene therapy (review: Adler et al., 1999). La Vail et al. have created eight different lines of transgenic rats, carrying either the P23H or the S334ter rhodopsin mutation (Nishikawa et al., 1997; Steinberg et al., 1997; Liu et al., 1999). The rats were produced by Chrysalis DNX, Princeton, NJ. Each line shows a different rate of photoreceptor degeneration. The reason for this is unknown. Two of these lines (S334ter line 3 and 5) are routinely used for transplantation of fetal retinal sheets (Sagdullaev et al., 2000; Seiler and Aramant, 2001).

2.2.4. *Models in larger animals*

Many transplantation studies have been done using normal rabbits (Seiler et al., 1990; Bergström et al., 1992; Ghosh et al., 1998) or cats (Huang et al., 1998) as

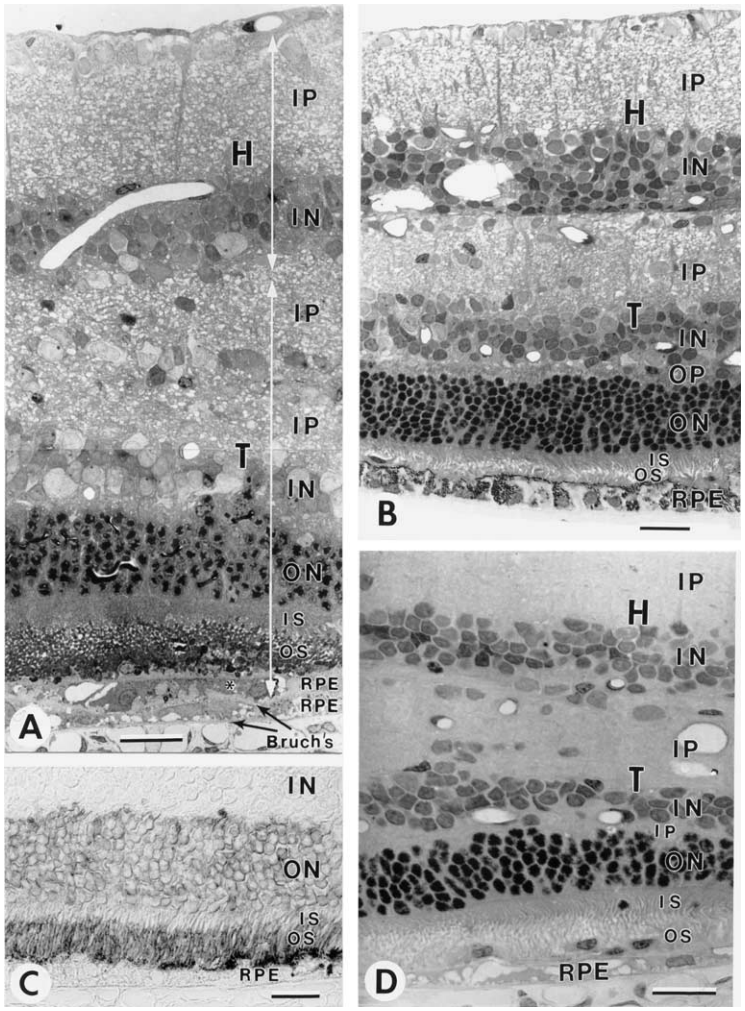

Fig. 2. Sheets of retina with or without its RPE transplanted to RCS rats. (A), (B), (C), cografts of retina with RPE; (D) transplant of retina only. (A) The outer nuclear layer of transplant contains ca. 6–7 rows of photoreceptors. The donor RPE cells (asterisk) can be seen on top of the host RPE cells. Note the good integration between transplant and host retina. Cograft of E19 retina with RPE to albino RCS rat, transplanted at 2.1 months. 3.7 months after transplantation. (B) Approximately 8 rows of photoreceptor nuclei. In contrast to the transplant in (A), this transplant shows a distinctive border towards the host. Note the monolayer of pigmented donor RPE. The choroid was dissected away during tissue processing. Cograft of E19 retina with RPE to albino RCS rat, transplanted at 1.8 months. 5.1 months after transplantation. (C) S-antigen staining of photoreceptor outer segments in cograft. The donor RPE has lost some of its pigment. E18 retina with RPE to RCS rat, transplanted at 1.4 months. 5.1 months after transplantation. (D) The donor RPE sheet was lost during transplantation. In spite of being confronted with dystrophic RPE of the RCS host, the transplant shows 5 rows of photoreceptors with outer segments. Note the microglia in the subretinal space. This transplant is well integrated with the host retina. E19 retinal transplant to RCS rat, transplanted at 1.8 months. 5.1 months after transplantation. Bars = 20 μm. (See Fig. 1 legends.)

recipients. So far, the only published retinal transplantation study in retinal degeneration models of larger animals was done by Gouras' group (Ivert et al., 1998) transplanting small pieces of 3–5 day old retina to the subretinal space of Abyssinian cats. These transplants developed rosettes. The recently developed transgenic pig retinal degeneration model (Li et al., 1998) has yet to be used for retinal transplantation.

Monkeys have been used as recipients for transplants of RPE (Gouras et al., 1984; Gouras et al., 1985; Sheng et al., 1995) and IPE cells (Abe et al., 2000a), but not as recipients of retinal transplants.

3. Retinal transplantation methods

3.1. Dissociated and microaggregate transplants

The earliest transplantation methods grafted small retinal pieces (aggregates) or dissociated cells. Because of the disruption of the donor tissue, retinal aggregate and cell suspension transplants invariably developed rosettes (Turner and Blair, 1986; Aramant et al., 1988; Del Cerro et al., 1989; Aramant and Seiler, 1991), i.e., spherical structures with the photoreceptors around an outer limiting membrane, inner and outer segments

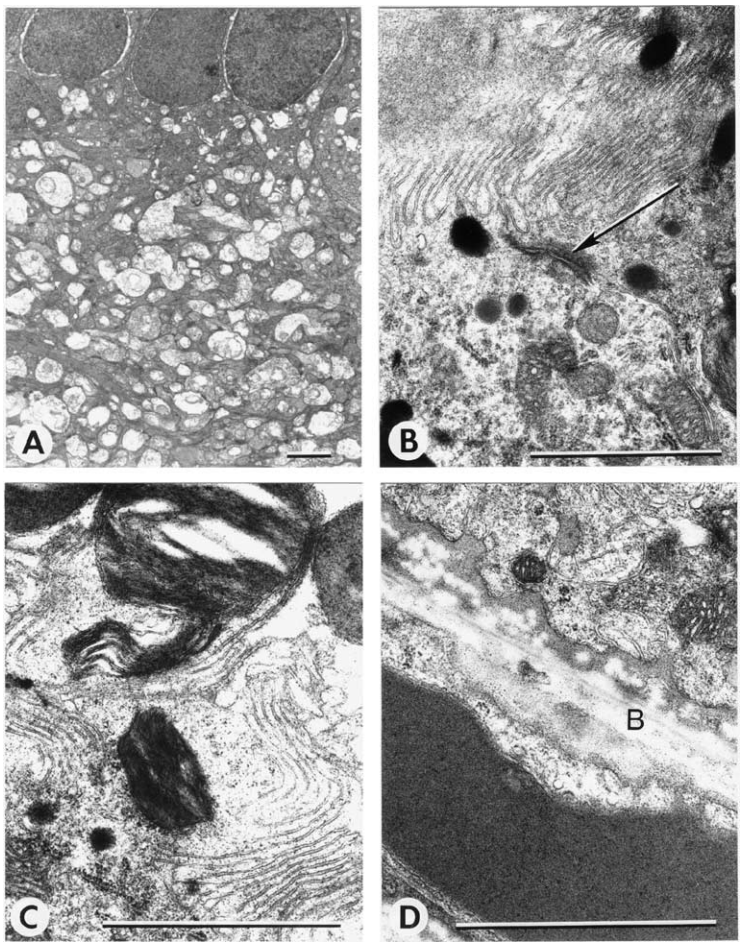

Fig. 3. Electron microscopy of retina/RPE cografts. (A) Transplant/host interface, showing the plexiform area between host inner nuclear layer and transplant inner plexiform layer. The exact border between transplant and host cannot be determined. (B) Tight junctional complex (arrow) between donor RPE cells. (C) Phagocytosis of outer segments. (D) Donor RPE cell with basal infoldings with mitochondria towards Bruch's membrane (B), with choroidal blood vessel underneath. (A) Same transplant as in Fig. 3A. (B), (C), (D): E20 transplant of retina with RPE to RCS rat, transplanted at 2 months. 1.7 months after transplantation. Bars = 2 μm. (See Fig. 1 legends.)

toward the lumen and with the inner retinal layers on the outside of the rosette, and abnormal Müller cell development with a missing inner limiting membrane (Seiler and Turner, 1988). Aramant and Seiler have used the transplantation of retinal aggregates to a retinal lesion site as a model to study the development of rat and human retinal cell types (Aramant et al., 1990a, 1990b; Aramant and Seiler, 1994; Seiler and Aramant, 1994), and the outgrowth of neuronal processes and synapse formation between transplant and host (Aramant and Seiler, 1995a). After 8 months of cryopreservation, transplants of embryonic retina could survive and develop retinal layers (Aramant and Seiler, 1991). This paper also showed that the subretinal space appeared to be more favorable than the epiretinal space for the development of laminar organization of the transplants.

Gouras transplanted dissociated adult rods with outer segments, prelabeled with ^{3}H-thymidine, together with RPE cells to the subretinal space of adult RCS rats (Gouras et al., 1991a, 1991c) or rd mice (Gouras et al., 1991b). The photoreceptor cells remained dispersed, and could retain some outer segments at 1–2 months after transplantation. Interestingly, synaptic structures were observed in the host outer plexiform layer although their functional significance was not established. However, the numbers of surviving transplanted cells decreased with time after transplantation.

Gouras developed an improved technique, the microaggregate method that consisted of cutting the neonatal retina into pieces that were small enough to pass through an injection needle without further disruption. This way, some of the transplanted pieces were randomly placed with the right polarity and could develop photoreceptor outer segments towards the rd mouse host RPE (Gouras et al., 1994).

Recently, Kwan et al. showed that mechanically dissociated postnatal (P7–9) mouse retinal cells transplanted to 6–8 week old rd mice could develop relatively large areas of photoreceptors in contact with the host

RPE (Kwan et al., 1999). The transplants formed a second synaptic layer at the graft/host interface in which rod spherules could be found. The authors could not exclude the possibility that the transplant photoreceptor synapses were with transplant bipolar cells. In addition, transplanted mice showed a return to a normal light/dark preference at 2 weeks after transplantation. The authors suggested that this might indicate the development of synaptic circuitry between transplant and host.

3.2. Transplants of retinal sheets

3.2.1. Photoreceptor sheets

Silverman developed a procedure to isolate photoreceptor sheets from adult and postnatal day 8 rat retinas by vibratome sectioning retinal wholemounts and transplanting them into the subretinal space (Silverman and Hughes, 1989a; Silverman et al., 1992). The transplanted photoreceptors could maintain their layered structure without forming rosettes only when part of the inner retina was included in the transplants, indicating the importance of Müller cells for photoreceptor organization (Silverman et al., 1991). This procedure was later refined by using an excimer laser to isolate human cadaver photoreceptors (Kaplan et al., 1997; Huang et al., 1998). Using Silverman's method, Sahel's group in Strasbourg has shown that photoreceptor sheets from normal mice can rescue cone photoreceptors in the rd mouse (Mohand-Said et al., 1997).

3.2.2. Full thickness retinal transplants to normal retina

Ehinger's group later adapted Silverman's method for transplanting whole fetal retina to normal rabbits (Ghosh et al., 1998, 1999a–c). A local retinal detachment was induced by a retinal bleb, the donor tissue was rolled up in the cannula of the instrument, and unrolled in the prepared space. If placed in the right polarity, such transplants developed all retinal layers and photoreceptors were in contact with host RPE.

However, this procedure involves trauma to the donor tissue and the host retina. The placement and polarity of the donor tissue apparently cannot be entirely controlled. Transplants of fetal rabbit retina, where the inner part had been shaved off by vibratome sectioning, developed rosettes; and it was claimed the donor tissue could sometimes "develop into laminated sections with reversed polarity" (Ghosh et al., 1999c). The reversal of polarity would be surprising, a more likely explanation is that the tissue was placed upside-down.

So far, Ehinger's group has not published any studies on transplantation of fetal retinal sheets into models of retinal degeneration. Since there are no suitable retinal degeneration models in the rabbit, these studies have their limitations. In addition, the rabbit host retina overlaying the transplant degenerates with longer survival times (Ghosh et al., 1999a, b). Because the rabbit retina is not vascularized, except for the central horizontal streak, its nutrition entirely depends on transport from the RPE. The insertion of the transplant between the RPE and the retina thus causes the degeneration of the host retina.

3.2.3. Fetal intact-sheet transplants to degenerated retina

Aramant and Seiler have developed a completely different approach to transplant intact sheets of fragile fetal tissue to the subretinal space (Aramant and Seiler, 1995b, 1996; Seiler and Aramant, 1998; Aramant et al., 1999), using a patented instrument and procedure (Aramant and Seiler, 1999, 2000b; Aramant, 2000). Using adult rats with retinal degeneration as recipients, they have demonstrated that an area of a damaged retina can be morphologically repaired by a sheet of fetal retina with or without RPE (Aramant and Seiler, 1995b, 2000b; Seiler and Aramant, 1998, 2001; Aramant et al., 1999). Details of these models and their results are further described below.

4. Morphological repair of damaged retinas by fetal neural retinal sheets

4.1. Advantages

Transplantation of intact sheets of fetal retina has some advantages over transplants of isolated (vibratome or laser sliced) postnatal photoreceptor sheets. The fetal donor retina contains pluripotent precursor cells that can develop into different retinal neuronal and glial cell types, depending on the microenvironment of the cell (Cepko, 1992). The Müller glial cells are important for the full development and maintenance of the photoreceptor cells (Rich et al., 1995; Willbold et al., 1997; Dubois-Dauphin et al., 2000). Postnatal and mature photoreceptors, transplanted as a sheet, maintain outer segments only if they are transplanted together with the adjoining part of the inner nuclear layer that contains Müller cells (Silverman et al., 1991, 1992). Photoreceptors of intact-sheet fetal transplants develop both inner and outer segments (Seiler and Aramant, 1998; Seiler et al., 1999b) and remain healthy for many months (see Fig. 1).

4.2. Procedure

The tissue is kept cold until transplantation. In most experiments, the fetal retina is flat embedded in a gel for protection. The patented method consists in flattening the tissue by capillary force without touching it (Aramant and Seiler, 1999). Recently, unembedded sheets of fetal tissue have also been transplanted (unpublished observations). The tissue is cut to the size

of the inner lumen of the flat implantation nozzle, which can be made in different sizes and shapes according to the size of the eye and the surgery approach. For a transplant into a rat eye, the size of the tissue is typically $0.8 \times 1.2\,mm^2$; for implantation into a human eye, the size of the piece can be $2 \times 3\,mm^2$. The tissue is picked up either by suction or backloaded in a window in the anterior part of the nozzle and is then locked in place. To reduce dead space of superfluous medium, the space in the tip of the nozzle can be easily adjusted according to the length of the donor sheet.

Compared to other methods, a minimal amount of medium is delivered to the eye. Thus, one can avoid an increase in pressure caused by the liquid that follows the donor tissue and which can push the tissue out again. Only a minimal bleb is necessary.

For transplantation into a rat eye, a small incision (0.8–1.2 mm) is cut behind the pars plana, and a local retinal detachment is produced. In larger eyes (such as humans), a transvitreal approach with vitrectomy and retinotomy is used (Radtke et al., 1999). The tip of the flexible silicon nozzle can have a different curvature depending on whether a transscleral or a transvitreal approach is used. After insertion of the instrument into the subretinal space, the nozzle is retracted over a fixed mandrel (non-movable plunger) which exposes the tissue and places it in the target area. Thus, the tissue is not pushed or injected into the site. During the delivery of the tissue, the instrument needs to be held completely still. In this way, the placement is entirely controlled by the surgeon.

4.3. Difficulties/requirements

However, in rats, only about one-third of the transplants to the subretinal space of degenerated retinas develop a lamination similar to normal retina, the rest will develop rosettes, sometimes with parallel layers (Seiler and Aramant, 1998). There are several reasons for this. Any damage to the host RPE, or any trauma to the donor tissue usually results in rosette formation. In the rat, the surgeon cannot see where the tissue is placed. The instrument nozzle has to be inserted at the right angle to avoid damaging Bruch's membrane or the host retina. If Bruch's membrane is damaged, the host RPE will be damaged, and/or part of the transplant might be placed into the choroid. A disruption of the RPE associated with the break of Bruch's membrane leads to a disruption of the outer blood retinal barrier, infiltration of the transplant with lymphocytes/macrophages and sometimes (but not always) transplant rejection. On the other hand, if the transplant is placed into the vitreous, it can also form rosettes. Sometimes transplants in the vitreous will be well organized with the exception that the photoreceptor outer segments degenerate.

When photoreceptor degeneration is too far advanced and has led to secondary changes in the RPE and choroid, the retina appears to fuse with the RPE. Under such circumstances, Bruch's membrane will be damaged during the insertion, the transplantation procedure is very difficult and the transplant will develop rosettes. If the host RPE is accidentally damaged by the implantation procedure, the transplant can still develop parallel layers, but not outer segments comparable to normal retina.

5. Co-transplantation of sheets of retina with its RPE—a method of choice in the future?

5.1. Advantages

Many retinal diseases involve degeneration of both photoreceptors and RPE. When the photoreceptors have irreversibly degenerated at later stages of the disease, transplantation of either RPE or photoreceptors alone might not be enough to restore vision. Transplant photoreceptors will develop fully and maintain outer segments if supported by RPE (Aramant and Seiler, 1995b; Seiler and Aramant, 1998; Seiler et al., 1999b). Therefore, in some diseases or stages of disease, retinal repair will require the transplantation of intact sheets of both RPE and neural retina.

5.2. Procedure

For preparation of the donor tissue, retina with its RPE, the fetal eyeballs are incubated in dispase (Collaborative Biomedical Products, Bedford, MA) (3–10 min for rat eyes, 30 min for human fetal eyes), and thoroughly washed afterwards. The enzymatic treatment makes it possible to peel the choroid off the RPE. After the RPE have been cleanly dissected, the retina with its RPE is cut into pieces, and vitreous and blood vessels at the inner surface of the pieces are removed (Aramant et al., 1999; Seiler and Aramant, 2000a, b).

5.3. Difficulties/requirements

The cografting of fetal retina with RPE poses an additional difficulty: the fetal RPE can easily loosen from the retina during removal of the choroid because the photoreceptor outer segments have not developed yet. It is more difficult to dissect rat fetal retina/RPE sheets compared to human. Freshly dissected rat retina/RPE sheets cannot be stored for more than 2–3 h; the RPE will start to contract and roll up. When the RPE sheet rolls up during or after transplantation, the transplants will contain RPE clusters that usually interfere with the ordered organization of the retinal transplant. Sometimes, the RPE sheet falls apart, and

dispersed RPE cells can be seen migrating through the retinal transplant. Nevertheless, transplants can be achieved in which the co-transplanted RPE stays as a monolayer, with tight junctions between the RPE cells, supporting the development and maintenance of the transplant photoreceptors (Figs. 2A–C). The reciprocal interaction between the donor RPE and retina might provide a better possibility for graft success than transplanting either tissue alone.

These results indicated that successful (i.e., well laminated) transplants require healthy RPE (either from the host or the donor) to develop normal appearing photoreceptor outer segments. However, transplants of retina-only have been observed in RCS rats that 5–7 months after transplantation still maintained outer segments in contact with the host RPE (see Section 2.2.1 and Fig. 2D).

What happens with the host RPE? In many cases, the host RPE is scraped off, and the donor RPE are sitting directly on Bruch's membrane with an apparently normal relation to the choroid (Fig. 3D). However, the presence of donor RPE on top of the host RPE or the development of a second basal lamina separating the two tissues appears to have no negative effects on the transplant photoreceptors (Fig. 2A).

6. Immunology

Allografts of fetal neuronal tissue have been shown to be immunologically tolerated in an adult host if attention is given to optimal donor parameters (e.g., donor age, storage medium, donor tissue preparation) (Widner and Brundin, 1988; Brundin et al., 1990; Dunnett, 1990; Koutouzis et al., 1994; Borlongan et al., 1996). Host immune responses against allogeneic fetal neural brain transplants were not sufficient to cause transplant rejection (Duan et al., 1995), and allogeneic fetal transplants survived better when a chemical inflammation was induced prior to implantation (Duan et al., 1998). However, examples of allograft rejection in the CNS have been described (Lund et al., 1989; Stein, 1991; Sinden et al., 1992; Borlongan et al., 1996; Brevig et al., 2000).

In the eye, the subretinal space has been shown to be an "immune privileged" site, similar to the anterior chamber and the central nervous system (Jiang et al., 1993; Grisanti et al., 1997; Wenkel and Streilein, 1998). This means that not only allografts of neonatal retina but also other foreign antigens do not elicit a classic immune response. The immune privilege of the subretinal space depends on the integrity of the blood–retinal barrier (Wenkel and Streilein, 1998).

Embryonic retinal allografts transplanted to a neonatal host brain are not rejected unless the host is challenged or the blood brain barrier is disrupted (Rao et al., 1989; Pollack and Lund, 1990). However, it has been shown that allogeneic subretinal transplants of postnatal mouse retina (cell aggregates) contain microglial cells expressing MHC class I and II antigens at 35 days posttransplantation (Ma and Streilein, 1998). These activated microglial cells are found in the center of rosettes in the retinal transplants. Larsson et al. did a similar study with syngeneic and allogeneic fetal retinal aggregate transplants to normal Lewis and Sprague Dawley rats (Larsson et al., 1999). With allogeneic transplants, there was a marked upregulation of MHC class I and II antigens in the transplant and the surrounding host retina. The authors hypothesized that some modification of the immune system prevented the allografts from being rejected. However, this issue needs further investigation.

Most of the microglial cells are associated with blood vessels and migrate into the retina postnatally in the rat (Ashwell et al., 1989) and from 16 weeks gestation in the human (Provis et al., 1997). The number of microglial cells in fetal rat retina is much lower than in postnatal retina (Ashwell et al., 1989). Therefore, it is likely that fetal retina is less immunogenic than postnatal retina because fetal retina still lacks inner retinal vessels. Unfortunately, most immunological studies done so far in the eye have not compared different donor ages. Stable intact-sheet fetal retinal transplants have been observed in rats 6–10 months after surgery. This indicates that allogeneic retinal sheet transplants can be tolerated in the subretinal space.

Many studies indicate that transplants of dissociated RPE cells to the subretinal space undergo chronic rejection (Algvere et al., 1999), and express MHC class I and II antigens after transplantation (Zhang and Bok, 1998). However, transplantation of intact sheets might have immunological advantages: allografted sheets of RPE, in contrast to dissociated cells, have been shown to be immunologically privileged—they are not rejected when transplanted to the kidney capsule (Wenkel and Streilein, 2000). Postnatal retinal tissue however was rejected.

7. Function and connectivity of retinal transplants

7.1. Function of transplant photoreceptors

Do retinal transplants contain functional photoreceptors? In order to achieve long term restoration of visual function, the transplant should develop normal cell layers and become integrated with the remaining healthy portions of the eye including both the RPE and the inner retina of the host.

Adolph recorded transient spike potentials and local ERGs from the surface of fetal aggregate subretinal grafts in vitro (Adolph et al., 1994). Another approach,

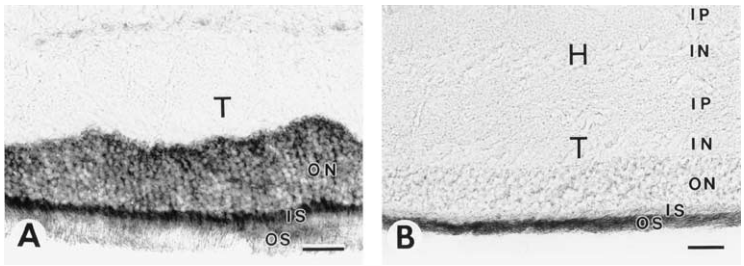

Fig. 4. Do transplant photoreceptors function normally?—Light–dark shift of rod α-transducin. (A) Transplant fixed in light. The transplant photoreceptors are clearly immunoreactive for α-transducin in the inner segments and less intense in the outer nuclear layer. The host RPE cannot be seen because of a tissue processing artifact. E19 donor, 2 months after transplantation. (B) Transplant fixed at the end of dark cycle. The main immunoreactivity has now shifted to the outer segments of the transplant photoreceptors. E18 donor, 2.4 months after transplantation. Bars = 20 μm. (See Fig. 1 legends.)

examining the light-dependent shift of signal transduction proteins (Whelan and McGinnis, 1988), was used to test photoreceptor function in retinal transplants (Seiler et al., 1999b). Subretinal intact-sheet transplants of fetal rat retinas to light-damaged albino rat eyes were fixed in light or dark. In light adapted transplants, rod α-transducin was predominantly found in inner segments (Fig. 4A). With dark-adaptation, transducin shifted to the outer segments (Fig. 4B). S-antigen distribution was opposite to transducin. Rhodopsin distribution did not change. The demonstration of a normal shift of signal transduction proteins indicated that normal phototransduction processes appear to be established in photoreceptors of transplanted retinal sheets (Seiler et al., 1999b).

7.2. Effects of retinal transplants on light reflexes and behavior

Del Cerro used an indirect behavioral test, the startle reflex, to show that retinal transplants have an effect on vision in light-damaged rats (Del Cerro et al., 1991). This test presents rats with a light a short time before they are startled by a loud sound. Normally sighted rats learn to associate the light with the sound; thus, the startle response will be reduced. Rats that have been trained in this test do not show a reduced startle response after exposed to light damage. However, rats with retinal aggregate transplants showed a reduced startle response, 20% of normal controls (Del Cerro et al., 1991). The author's hypothesis was that the transplanted rats could "see" the flash and expected the sound, and therefore reacted less.

Another test, the pupillary light reflex, has been successfully used to show the function of retinal transplants placed into the brain (Klassen and Lund, 1990; Radel et al., 1992; Radel et al., 1995). Silverman et al. reported that transplants of photoreceptor sheets restored the pupillary light response in light-damaged rats when compared with sham surgeries (Silverman et al., 1992). The pupillary reflex has also been used to assess the effect of RPE transplants in the RCS rat (Klassen et al., 2001). However, it appears that the intensity of the reflex is not correlated with the number of functional photoreceptors in the eye (Kovalevsky et al., 1995).

Del Cerro's group showed with the sensitive water maze test that RCS rats could learn this task after RPE transplantation whereas sham surgery and non-operated control RCS rats could not (Little et al., 1998). The test performance is generally correlated to the number of photoreceptors (Spencer et al., 1995) although this is not the case for rats with severely damaged retinas (O'Steen et al., 1995).

R.D. Lund's group has used a variety of tests to show the effects of transplants on visual behavior. For example, Kwan et al. used a light–dark preference test to demonstrate that after transplantation of dissociated postnatal retinal cells to rd mice the preference for the dark compartment is restored (Kwan et al., 1999). It would have been interesting to see whether this effect was present for a longer time than 2 weeks after transplantation.

Head tracking and visual acuity tests are reliable methods for assessing visual function in pigmented rats and can show different aspects of retinal degeneration (Hetherington et al., 2001) and photoreceptor rescue after RPE transplantation (Coffey et al., 2001; Lund et al., 2001). However, this test has not yet been used for testing retinal transplants to the retina.

7.3. Electrophysiological evidence for retinal transplant function

Using aggregate transplants to rd mice, ganglion cell responses were recorded over the transplant in 3 of 10 mice (Radner et al., 2001) that had received transplants at the age of 13 days. No responses were found in sham surgeries, or in mice that had received transplants at the age of 8 weeks. These results indicated that the stage of degeneration of the host retina is an important determinant of the functional capacity of transplants.

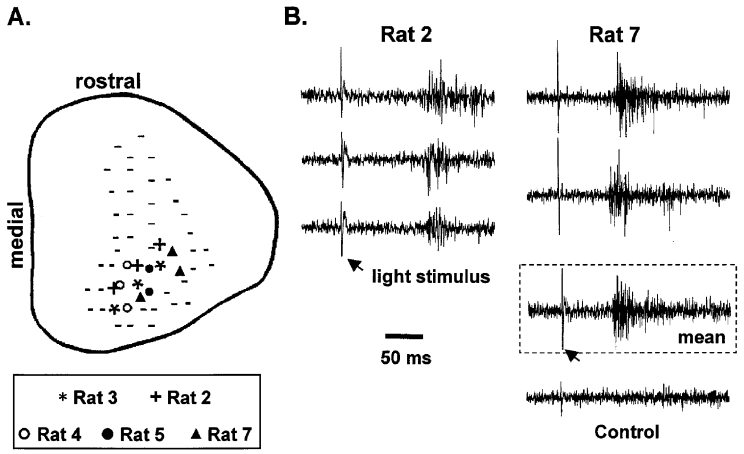

Fig. 5. Transplants restore visual responses in RCS rats. Multi-unit electrophysiological recordings from the superior colliculus, contralateral to the transplanted eye. (A) Recording examples of the first 5 of the 19 transplanted rats with visual responses, showing the location of sites from which visually evoked (+) or no visual response (−) could be elicited. The visually responsive area in the SC corresponds to the location of the transplant in the nasal/dorsal retina. (B) Examples of single sweeps (500 ms duration) recorded from two rats, 3.5–4.8 months after transplantation. An average of 16 sweeps at one location also is shown (mean). Taken from Fig. 2 of Woch et al., 2001. Reprinted with permission. Copyright holder—Association for Research in Vision and Ophthalmology.

Silverman recorded visually evoked potentials (VEPs) in light-damaged rats with photoreceptor sheet transplants (Silverman et al., 1992). Unfortunately, his results were not independently confirmed by others.

The well-known topographical representation of different retinal areas in the superior colliculus (Siminoff et al., 1966) has been used to show the loss of visual sensitivity with age in the RCS rat (Sauvé et al., 2001) and to demonstrate the functional effect of photoreceptor rescue after grafting RPE or Schwann cells to 3–4 weeks old RCS rats (Sauvé et al., 1998; Lawrence et al., 2000).

This method was used to show that sheets of retina with RPE transplanted to 5–7 weeks old RCS rats can restore visual responses in an area of the superior colliculus that topographically corresponds to the placement of the transplant in the retina (Woch et al., 2001) (Fig. 5). Although faint responses were recorded in some sham surgeries, the amplitudes of the responses from the transplants were significantly different, and more similar to normal controls. However, transplant responses had a longer latency than normal controls. Similar results were seen in transgenic rats (S334ter, line 3) with rapid photoreceptor degeneration (Sagdullaev et al., 2000) (manuscript in preparation) although these responses do not directly address the issue of connectivity.

7.4. Morphological indications for transplant–host connectivity

Subretinal intact-sheet transplants can integrate well with a degenerated retina (examples in Figs. 1, 2 and 3a), in contrast to subretinal transplants to normal retinas (Aramant and Seiler, 1991). This is likely due to the fact that the inner retinal neurons in a retina with photoreceptor degeneration are deprived of synaptic inputs from the photoreceptors. Retinal injury has been shown to induce upregulation of trophic substances (Cao et al., 1997, 2001) that attract fiber ingrowth in several systems (Unsicker et al., 1992; Lewis et al., 1998; Lewis et al., 1999). In addition, the embryonic cells can produce factors that can act as signals on responsive denervated neurons (Hadani et al., 1984; Hausmann et al., 1989; Gravina et al., 1990; Bennett et al., 1999).

After transplantation of intact fetal retinal sheets, both the transplant and the host have an inner nuclear layer. How can the transplant and host interneurons interact? The wiring would be different from a normal retina, e.g., a transplant bipolar cell might contact a host bipolar cell. To what degree is the duplication of inner retinal neurons an obstacle for appropriate connections between transplant and host, or will the host retina and brain be able to obtain appropriate information from an abnormal circuitry?

Previously, it was demonstrated that embryonic aggregate transplants can grow neural processes and form synapses within the host retina (Aramant and Seiler, 1995a). Integration of intact-sheet transplants with the host retina varies (examples in Figs. 1, 2 and 3A). Integration of the inner plexiform layers of transplant and host can be observed, and neuronal processes of transplant and host cells appear to cross the interface between transplant and host (Seiler et al., 1999a, 2001) (Fig. 1C). This indicates that synaptic connectivity is possible. Synaptic connections between transplant and host retina are also suggested by transsynaptic tracing from the host brain to the transplant

(Aramant et al., 2000) (manuscript in preparation) using an attenuated pseudorabies virus which is specifically transferred from one neuron to the next at synaptic contact points (Card, 1998).

8. Xenografts of human fetal tissue

8.1. Aggregate transplants

In the past, human retinal cell aggregates were transplanted to immunosuppressed rats to obtain a model for human retinal transplant development (Aramant et al., 1990b; Ehinger et al., 1991; Seiler et al., 1991). Using different retinal cell markers, it could be shown that such transplants develop most of the retinal cell types according to the human timetable (Seiler and Aramant, 1994). Aggregates of human fetal retina have also been transplanted to the anterior chamber of immunosuppressed rats (Epstein et al., 1992). Later, the use of the athymic "nude" rat as a recipient for the transplantation of human embryonic retinal cells was investigated (Aramant and Seiler, 1994). Nude rats offer an excellent model for the study of human retinal xenografts without the negative effects of immunosuppression. Compared to immunosuppressed rats, transplantation to nude rats gave consistent results and superior long-term survival of hosts and transplants.

8.2. Sheet transplants

After establishing the intact-sheet transplant model in rats with retinal degeneration (Aramant and Seiler, 1995b, 2000b; Seiler and Aramant, 1998, 2001; Aramant et al., 1999), a study was started to investigate whether cografts of human fetal retina and RPE to nude rats could develop and maintain their cytoarchitecture after long survival times to obtain data for preparation of clinical trials. In 4 of 11 transplants, the RPE stayed as a monolayer sheet and supported the development of the retinal sheet with a normal lamination, including photoreceptor inner and outer segments (Seiler and Aramant, 2000a, b) (manuscript in preparation). These results suggested that co-transplantation of fetal retina with RPE might also be feasible in human patients.

9. Clinical trials

9.1. RPE and IPE transplantation

The success of RPE transplants in RCS rats has led to clinical trials in AMD patients by a team in Sweden in collaboration with Columbia University, NY (Algvere et al., 1994, 1997, 1999). The first transplants were carried out on 5 patients with end stages of macular degeneration ("wet" form of the disease) (Algvere et al., 1994). The transplants showed signs of rejection within 3 months. The authors reported a better success in clinical trials with 9 patients that had a less severe stage of the disease ("dry" form): 4 patch transplants, and 5 transplants of dissociated cells (Algvere et al., 1997, 1999). In 5 of 9 eyes, signs of rejection were seen after 6–20 months. However, 3 of the 4 RPE patch transplants to the "dry" AMD patients were not rejected.

To overcome the rejection problems with allogeneic RPE, different groups have performed autologous transplants of adult RPE cells (Binder et al., 2001) and iris pigment epithelial (IPE) cells (Abe et al., 2000b; Thumann et al., 2000), mostly to patients with "wet" AMD. Subjective improvements in visual acuity were reported.

9.2. Retinal transplantation

Aggregates of fetal retinal cells have been transplanted to RP patients in India (Das et al., 1999) and to eight RP and one AMD patient at Johns Hopkins University (Del Cerro et al., 2000; Humayun et al., 2000). The Das group reported some subjective improvements. No lasting improvements were noted by Humayun's group. No adverse effects or rejection were reported. Similarly, sheets of human cadaveric photoreceptors were transplanted to two RP patients with no adverse effects (Kaplan et al., 1997). No improvements were noted, but also no rejection.

Sheets of fetal retina without RPE were transplanted to 4 retinitis pigmentosa patients. One of these patients transiently showed a faint positive response in the multifocal ERG (Radtke et al., 1999). After obtaining an Investigational New Drug Application (IND) number from the Food and Drug Administration (FDA), additional trials have started to transplant sheets of fetal retina together with its RPE to five retinitis pigmentosa patients that had only light perception (Radtke et al., 2001) (manuscript in preparation). Patients that have only light perception are in the endstage of their disease and can only distinguish between light and dark. These trials demonstrated that the procedure is safe. No rejection has been observed, as would be indicated by fluorescein leakage.

10. What is next?

Fetal retinal sheet transplants, without and with their RPE, can morphologically integrate into a degenerated rat retina, and restore visual responses in the superior colliculus. There are also indications that synaptic connections exist. However, it needs to be unequivocally demonstrated that transplants make functional synaptic connections with the host retina. This needs to be shown

in several ways: morphologically by tracing and electron microscopy, electrophysiologically and by behavioral tests. An unequivocal label of the cytoplasm of the donor cells would also be helpful to demonstrate synaptic connections.

If the transplants can develop a circuitry with the host retina as the data indicate, this circuitry probably needs to be improved. It might be argued that the retinal interneurons in the transplant can interfere with the synaptic connectivity of transplant photoreceptors with the host retina. Removal of the surface of the donor retina might eliminate cells that interfere with the circuitry, and increase the connectivity between transplant and host. Another route would be treatment with trophic factors, or gene delivery into donor cells. This has to be done with carefully selected control experiments since the host retina upregulates different factors after injury (Cao et al., 2001).

In intact-sheet cografts of retina with RPE, it is likely that the donor RPE cells produce many trophic factors that influence the donor and host retina, as they do during normal development (Raymond and Jackson, 1995; Tombran-Tink et al., 1995). Although cografting is more difficult than grafting of retina alone, it has the advantage of providing the fetal donor retina with the trophic factors produced by the RPE.

Growth factor and gene therapy can help to delay retinal diseases, but once photoreceptors are lost, retinal transplantation remains the only hope.

Sufficient progress has been made which indicates that retinal transplantation is a viable approach. While much still needs to be done, given the time and resources, there is every indication it will succeed in the future. To be successful, every research project needs long-term commitment and support.

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