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Retinal transplants evaluated by optical coherence tomography in photoreceptor degenerate rats

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Abstract

Optical coherence tomography (OCT), a non-invasive method, was used for qualitative assessment of fetal retinal sheet transplants by non-invasive imaging. Rhodopsin-mutant S334ter-line-3 rats with fast retinal degeneration (28–37-day old) were transplanted with fetal retinal sheets from embryonic day (E) 18–19 pigmented normal rats. Retinal thickness measurements from transplanted ($n = 51$), no surgery control ($n = 8$), and normal pigmented rat eyes ($n = 6$) were obtained using a Zeiss stratus OCT-3 scanning instrument. Frozen retinal sections were stained with hematoxylin/eosin. S334ter-line-3 rats showed significant reduction in OCT retinal thickness ($p < 0.001$) compared to normal pigmented rats at the age of 21 days. In 62% of the transplanted rats, OCT scanning revealed the presence of a subretinal graft, which was confirmed by subsequent histology. Retinal thickness in the transplant area was significantly increased compared to the area outside the transplant and to non-transplanted eyes ($p < 0.001$). While most of the transplants with single-band OCT images (87%) had rosetted transplants, a considerable proportion of transplants having a multi-band OCT image were found to have well-laminated areas in the graft after histological evaluation. Following retinal transplantation in rodents, OCT imaging data correlated mostly with transplant morphology. OCT is a useful technique for in vivo screening and evaluation of retinal transplants. This technique determines surgical outcomes at a much earlier stage.

Keywords: Retinal imaging; Retinal degeneration; Eye; Optical imaging; Transplantation

1. Introduction

Optical coherence tomography (OCT) is a non-contact, non-invasive optical imaging technique that has been widely used in the clinic since its introduction by Huang et al. (1991). More recently, the technique has been used in animal models as a useful tool to assess native as well as iatrogenic retinal defects (Toth et al., 1997a,b; Ge et al., 1999; Ducros et al., 2001; Fukuchi et al., 2001; Horio et al., 2001; Li et al., 2001; Gloesmann et al., 2003). Recent investigations in mice demonstrate the reliability of OCT imaging to measure retinal thickness at various stages of retinal degeneration (Horio et al., 2001; Li et al., 2001).

Retinal transplantation has been studied as a potential therapeutic strategy for preservation of vision in retinal degenerative diseases (Lund et al., 2003; Aramant and Seiler, 2004). In rats, intact sheets of fetal retina can be transplanted into the subretinal space of retinal degenerate rats to restore the damaged retina (Seiler and Aramant, 1998). Recently, comparable techniques have been employed in human patients with progressive retinal degeneration (Radtke et al., 2002, 2004; Berger et al., 2003). In Royal College of Surgeons

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(RCS), rats (Woch et al., 2001), S334ter-line-3 transgenic rats with fast retinal degeneration (Sagdullaev et al., 2003), and S334ter-line 5 transgenic rats with slow retinal degeneration (Thomas et al., 2004), transplantation of retinal sheets resulted in considerable improvement in visual responses in the superior colliculus in an area corresponding to the placement of the transplant in the retina. In S334ter-line-3 and 5 rats, it was also shown that restoration of visual responses in the superior colliculus is mostly observed in rats with better laminated transplants (Sagdullaev et al., 2003; Thomas et al., 2004).

However, despite the advances in transplant surgery and use of minimally traumatic techniques, only 30% of transplant procedures yield well-laminated grafts. In the remaining cases, grafts are present in ectopic locations (epiretinal or choroidal), grafts show poor morphology (disorganization or extensive rosettes), or significant areas of retinal detachment are present—all of which are surgical outcomes unlikely to yield positive functional results. Efficient methods to assess the surgical outcome at an early stage could facilitate the evaluation of retinal transplants, by eliminating the need for animals with poor transplant morphologies to undergo extensive, unproductive testing.

Up to now, a reliable evaluation of the transplanted cells or grafts was performed only after the animals were sacrificed for conventional histology. Consequently, animals with defective surgeries were also subjected to a battery of complex functional tests, which were subsequently found to be of little value after histologic analysis was complete.

The present study evaluates the usefulness of the OCT scanning technique in assessing surgical outcomes following transplantation.

Pigmented S334ter-line-3 transgenic rats that express an altered human rhodopsin protein (Liu et al., 1999; Sagdullaev et al., 2003), were used as recipients for retinal transplants. At the age of post-natal day (P) 28, the outer nuclear layer of these rats consists of only one row of photoreceptor cell bodies. OCT scan profiles were obtained from transplanted and non-transplanted eyes of transgenic rats as well as from normal pigmented rats, and were correlated with the corresponding histological findings.

2. Materials and methods

2.1. Animals

Animals were maintained in accordance with the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmologic and Vision Research, and institutional approval was obtained. For all surgical and OCT procedures, the animals were anaesthetized by intraperitoneal injection of ketamine and xylazine (37.5 and 5 mg/kg, respectively) and pupils were dilated with 0.5% phenylephrine hydrochloride and 0.5% tropicamide.

For the evaluation of retinal thickness, 21-day-old normal pigmented ($n = 6$) and transgenic pigmented S334ter-line-3 rats ($n = 8$) were used. Founder breeding pairs of the transgenic rats were produced by Chrysalis DNX Transgenic Sciences, Princeton, NJ, and kindly provided by Dr. M. M. LaVail, UCSF, San Francisco, CA. Rats for transplantation studies (21–23-day-old) were exposed to blue light for 5 days to accelerate the photoreceptor degeneration. The light damage (LD) treatment was aimed at reducing residual visual responses by eliminating the surviving photoreceptors, although preliminary OCT scan data revealed that in S334ter-line-3 rats, the LD treatment did not cause further reduction in the retinal thickness. At post-natal days (P) 31–41, the LD-treated rats ($n = 49$) received retinal sheet transplants. The donor tissue was derived from embryonic days (E) 18–19 pigmented normal transgenic rats that expressed human alkaline phosphatase (hPAP) in the cytoplasm of all cells. Forty-seven rats received transplants in the left eye, and two rats received transplants in both eyes. Transplants were placed in the subretinal space, in the superior-nasal quadrant of the host eye as described previously (Seiler and Aramant, 1998; Aramant and Seiler, 2002; Sagdullaev et al., 2003). Light-damaged S334ter-3 rats without surgery ($n = 12$) served as controls. OCT scan images were obtained from all 51 transplanted eyes. Histology data were not available for one transplanted eye that was damaged during dissection. Therefore, information regarding 50 eyes was included in the final data. An overview of the experiments is shown in Table 1.

2.2. OCT imaging

Cross-sectional imaging with radial line scans of the retina was performed using the Stratus OCT (OCT-3) Instrument (Carl Zeiss Meditech Inc. CA, USA). The OCT3 projects a broad bandwidth light beam (820 nm) onto the retina to obtain retinal anatomy with axial resolution of $\leq$10 μm and transverse resolution of 20 μm. The anaesthetized rat was placed on an adjustable holder that could be rotated easily. During the initial scanning, all eyes were positioned at a 90° angle with respect to the beam of the scanner. Scanning in this angle results in scans mostly from the central area of the retina. For exploring the other retinal areas, the position of the eye was changed by turning the rat holder. Generally, a graft if present could be located during the initial scanning. On the other hand, when no graft was located, scanning was continued for up to 15 min, with continuous re-positioning

Table 1
Classification of S334ter-line-3 transplanted rats based on OCT data

OCT image	Number (%)
Good	31 (62)
Multi-band	15 (30)
Single-band	16 (32)
Poor	19 (38)
Graft absent	12 (24)
Graft displaced	7 (14)

of the rat to allow scanning of all accessible retinal regions. Once the graft was located, horizontal and or vertical OCT scans were performed, based on the orientation of the graft. OCT scanning in 35 rats (35 eyes) was performed 2 and 6 weeks after surgery. The remaining 14 rats (16 eyes) were scanned only once at 6 weeks after surgery. Retinal thickness was measured from OCT images using the OCT scan profile. The OCT3 calculates the retinal thickness as the distance between the vitreoretinal interface and the anterior surface of the RPE/choriocapillary region. In all rats, the thickness of the retina was averaged from three scan images (obtained from the central area) each representing the superior, inferior, and the median sides. For each scan image, the retinal thickness value was averaged from three different locations of the image representing the center and the two sides (nasal and temporal sides). Thus, for each eye, the final value representing the retinal thickness was obtained from the average of nine (3×3) individual measurements. For transplanted rats, all measurements were made from the area containing the graft.

2.3. Histology

Eye cups were fixed in 4% paraformaldehyde in 0.1 M sodium phosphate buffer, infiltrated with sucrose, and frozen in tissue tek on dry ice. Series of transverse 10 μm sections of the retina were cut on a cryostat. Transplanted eyes were cut from the beginning until the end of the graft area. Based on the size of the graft, 30–70 slides (three sections per slide) were obtained from each eye and every 5th slide was stained histochemically for the presence of human placental alkaline phosphatase to visualize the grafted cells (data not shown). Selected slides were stained with hematoxylin–eosin (H&E) and photographed, using a SPOT RT digital camera on a Nikon FXA microscope. Slides from the mid-peripheral area of the retina were selected for measuring the full retinal thickness (from inner limiting membrane to RPE) using the SPOT image acquisition software. For each rat, the retinal thickness was measured from three different sites of each of several images (center and the two sides).

2.4. Statistical analysis

Using Graphpad Software (San Diego, CA, USA), a paired *t*-test was performed for comparison between eyes of the same animal and an unpaired *t*-test for comparison between eyes of different animals.

3. Results

3.1. OCT scanning

Horizontal bands representing various retinal layers were observed in the OCT scan images from normal pigmented rat retina (Fig. 1A). The appearance of the bands was based on the differential reflection properties of the various layers (and interfaces) of retinal tissue. Retinal thickness measured with the OCT (Fig. 1B and C) corresponded well to thickness measurements in histological sections (Fig. 1D). In retinal degenerate S334ter-3 rats, the thickness and number of retinal bands were considerably reduced (Fig. 1E–H).

OCT scan images from transplanted S334ter-3 rats showed horizontal moderately reflective band(s) below the host retina at the transplant site. Based on the quality of these bands, the retinal transplants were classified into three categories: (1) multi-band transplant (two to four horizontal bands in the transplant area, Fig. 2A and B); (2) single-band transplant (only a single horizontal band observed below the host retina at the transplant site, Fig. 2C); (3) displaced or absent transplant (no graft or graft placed in the choroid or epiretinal space, Fig. 2D and E). Based on this classification, 30% (15/50) of the transplanted rats had multi-band grafts and 32% (16/50) had single-band grafts. The remaining 38% (19/50) of the transplanted rats had displaced transplants (Table 1).

3.2. Retinal thickness

The reliability of OCT images to detect retinal thickness and morphology was evaluated in normal pigmented rats and LD treated rhodopsin-mutant S334ter-line-3 retinal degeneration rats. Compared to the normal rats (Fig. 1A–C), OCT data obtained from 35-day-old S334ter-line-3 rats (Fig. 1E–G) revealed a significant reduction in retinal thickness ($p < 0.0001$). This observation was consistent with the histology data (Table 2) showing a considerable reduction in the number of photoreceptors in the outer nuclear layer of 35-day-old S334ter-line-3 rats (Fig. 1H).

The thickness of the retina in the transplant area was evaluated from 21 rats with subretinal grafts at two different time periods after transplantation surgery. All these rats

Table 2
Comparison between OCT image and histology of 21-day-old normal and 35-day-old S334ter-line-3 rats light damaged to accelerate photoreceptor degeneration (mean ± S.D.)

	OCT data	Number of animals	Histology data	Number of animals
S334ter-line-3 rats	93.8 ± 6.0	5	108.6 ± 3.9	2
Normal rats	217.1 ± 9.9	6	235.2 ± 12.1	1

Using the OCT scan profile, the retinal thickness (distance between the vitreoretinal interface and the anterior surface of the RPE/choriocapillary region) for each rat was averaged from three scan images—the superior, inferior and the median. Thickness of each scan image was averaged from three different locations representing the center and the two sides (nasal and temporal). For histology data, mid-peripheral areas of the retina were selected for measuring the full retinal thickness (from inner limiting membrane to RPE) using the SPOT image acquisition software. For each rat, the retinal thickness was averaged from three different sites of the images (center and the two sides). For the normal rat, the retinal thickness value is the average of 30 measurements from 10 images. For the transgenic rats, the retinal thickness value is the average of 15 measurements of five images.

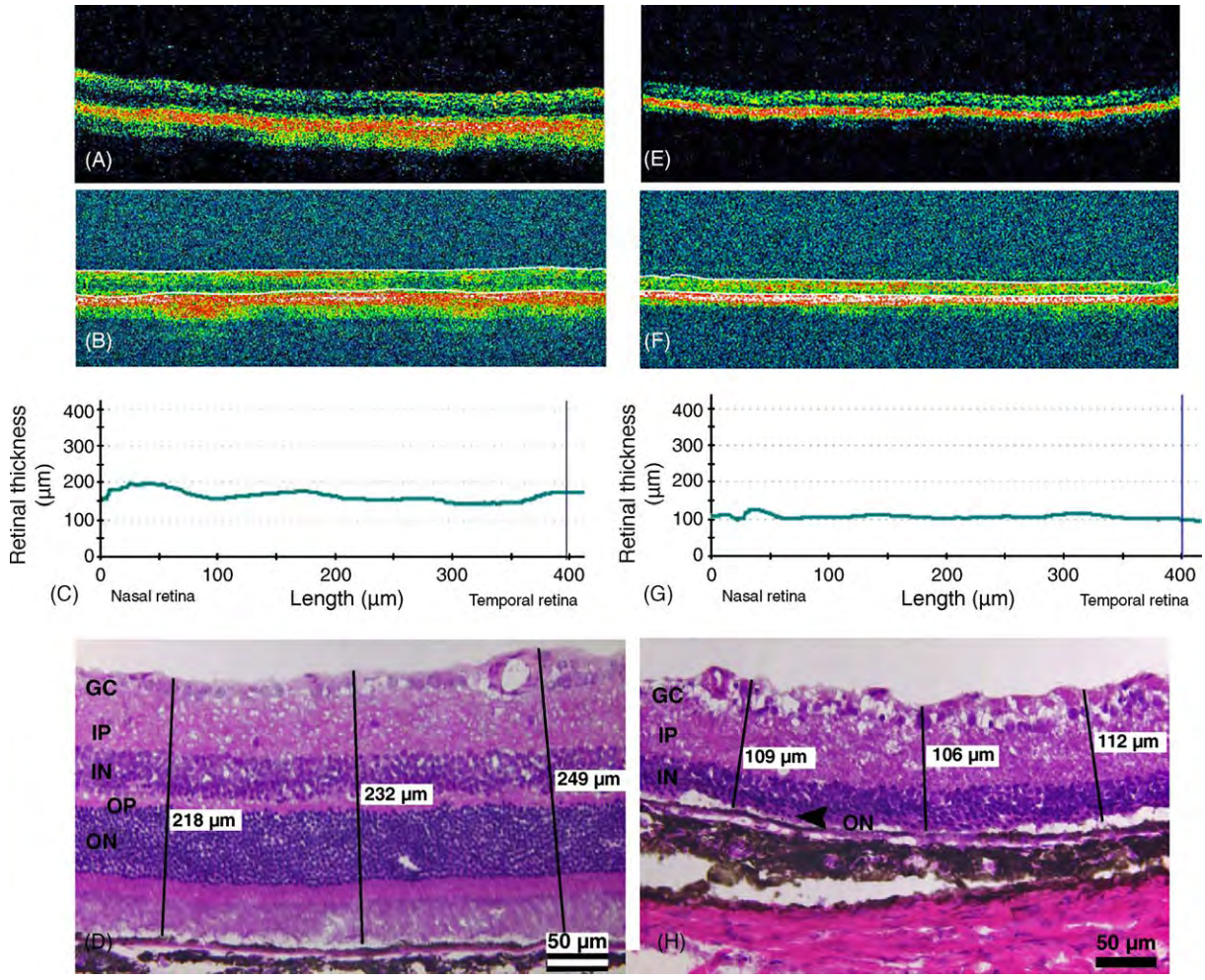

Fig. 1. Comparison of optical coherence tomogram (OCT) with histology of a 21-day-old normal pigmented rat (A–D) and a 35-day-old retinal degenerate light-damaged S334ter-line-3 rat (E–H). An area near the central retina was selected for both OCT and histology evaluations: (A and E) the OCT image; (B and F) retina thickness measured using the OCT scan profile (distance between the vitreoretinal interface and the anterior surface of the RPE/choriocapillary region indicated by the black arrow); (C and G) the graphical representation of the OCT scan data; (D and H) the corresponding histology images showing that thickness measurements of the OCT approximately correspond to the measured thickness of the histological sections. For histology data, the full retinal thickness (from inner limiting membrane to RPE indicated by the bold line) was measured using the SPOT image acquisition software. GC, ganglion cell layer; IP, inner plexiform layer; IN, inner nuclear layer; OP, outer plexiform layer; ON, outer nuclear layer. Scale bars, 50 μm.

were scanned twice. When scanned 2 weeks after transplantation surgery, the retinal thickness at the transplant area was 237 ± 8.15 μm. At 4 weeks after surgery, the retinal thickness was 212 ± 16.0 μm. This reduction in retinal thickness at the transplant area was also found to be statistically significant ($p < 0.001$).

3.3. Gross examination of fixed eyes

After fixation, eye cups were studied under a dissection microscope before embedding. Sixty percent (30/50) of the transplanted eyes contained a graft in the subretinal space. In the remaining 40% (20/50), the transplant was either displaced in the choroid, the epiretinal space or not found. According to the OCT data, a subretinal graft was present in 62% (31/50) of the transplanted eyes while the remaining 38% (19/50) belonged to the "poor" transplant group (Table 1) which included 12 (24%) without any graft and 7 (14%) having displaced transplants. One of the eyes from the "no graft" group when examined during dissection contained a very small subretinal graft.

3.4. Correlation between OCT and histology data

Histologic evaluation revealed a significant correlation between multi-band OCT images and laminated grafts (Table 3); 47% (7/15) of the transplanted eyes with a multi-

Table 3
Comparison between OCT image and histology data of rats with "good" transplants ($n = 31$)

Groups	% of laminated grafts (*N*)	% of rosetted grafts (*N*)
Multi-band OCT	47 (7/15)	53 (6/15)
Single-band OCT	12 (2/16)	87 (14/16)

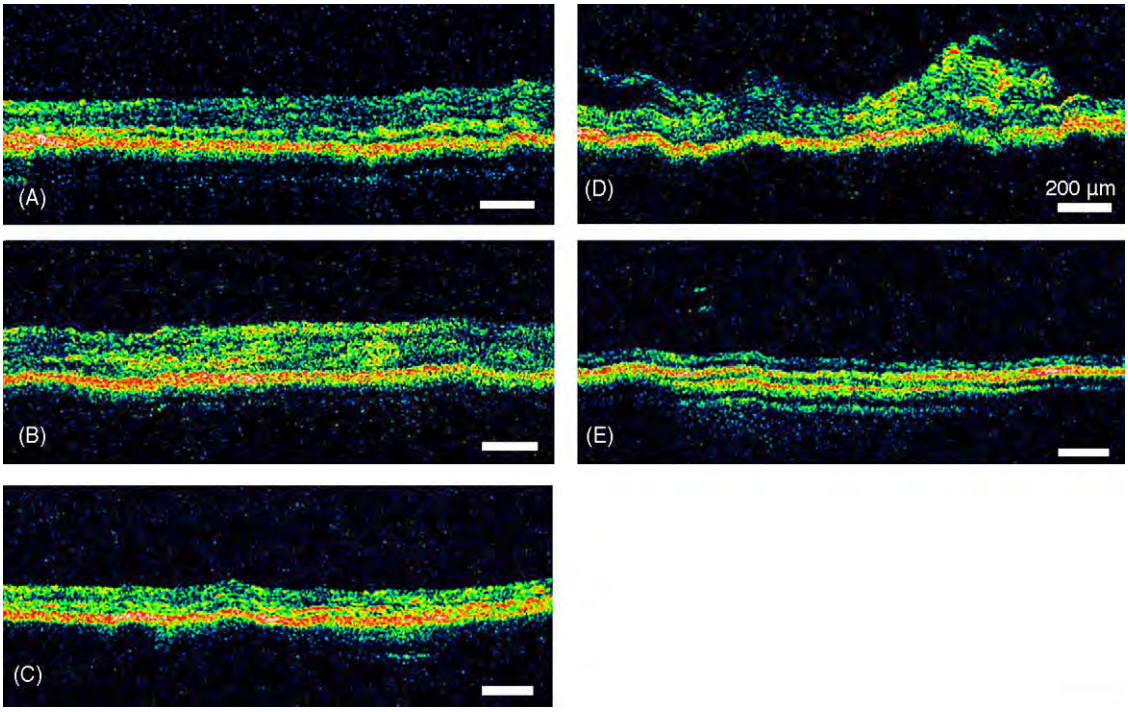

Fig. 2. Examples of optical coherence tomograms of transplants: (A) multi-band laminated transplant; (B) multi-band rosetted transplant; (C) single-band rosetted transplant; (D) displaced epiretinal transplant; (E) displaced transplant in choroid. The OCT images of the transplants that contained mostly rosettes contain more high reflection areas. Each figure shows a different transplant.

band graft in the OCT image were found to contain well-laminated areas in the transplant upon histologic evaluation (Fig. 3A and B). However, some transplants that appeared well-laminated in the OCT (Fig. 3C) contained rosettes in the outer nuclear layer, whereas the inner part of the transplant appeared well-laminated (Fig. 3D). Other multi-band transplants contained rosettes, which also appeared to be evident on the OCT (Fig. 4A and B).

In contrast, only 13% (2/16) of the single-band grafts (Fig. 4C and D) showed any laminated areas in the graft.

3.5. Retinal detachment

Five transplanted eyes showed a wide area of retinal detachment in the OCT image (Fig. 5A and C). These detachments, which presumably persisted from the time of trans-

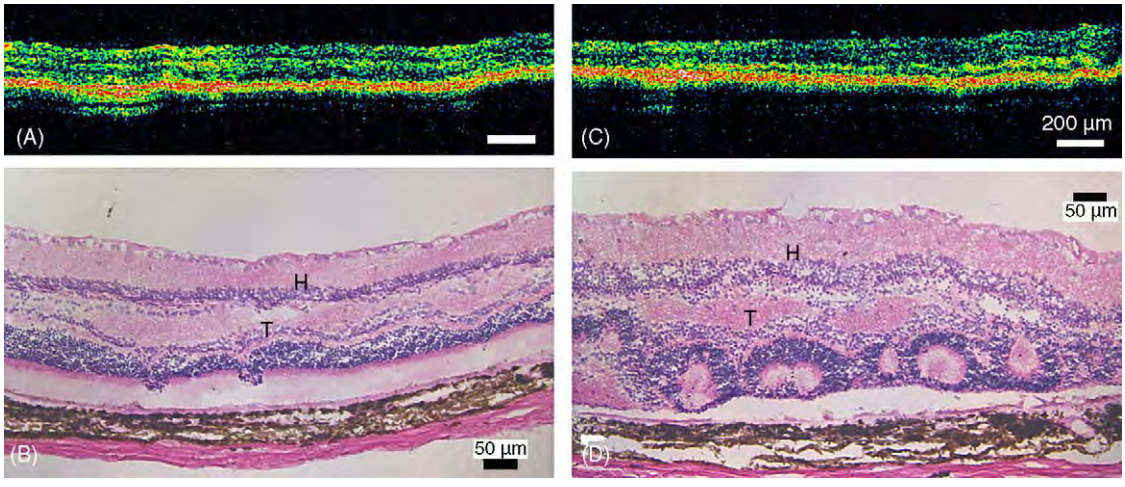

Fig. 3. Histologic correlation of laminated multi-band transplants. Optical coherence tomograms (A and C) and histology (B and D) of a laminated (A and B) and partially rosetted–partially laminated transplant (C and D). Note that the OCT images in (A and C) look similar. Although the inner retinal layers of the transplant in (C and D) are laminated, the transplant contains only rosettes in the outer nuclear layer. H, host; T, transplant. Bars = 50 µm.

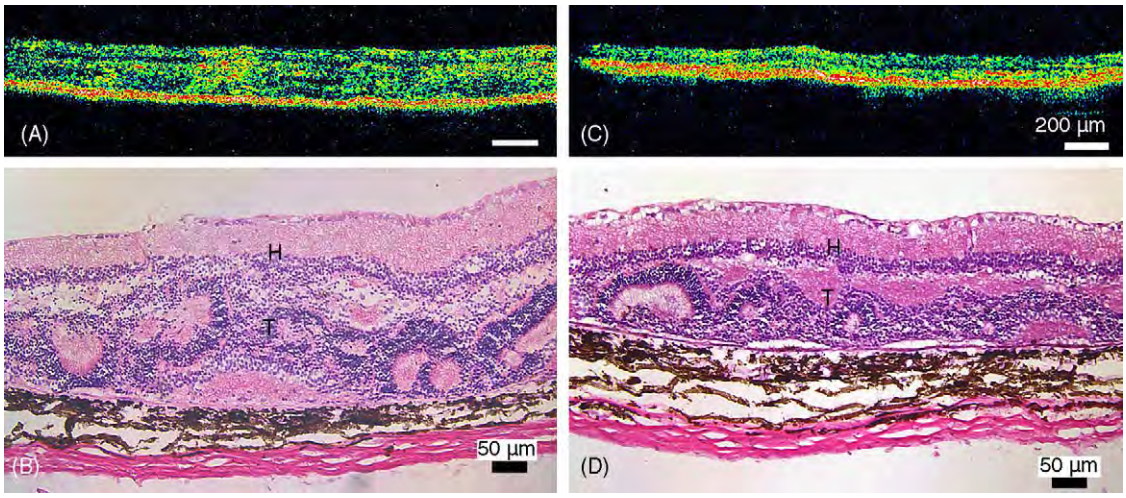

Fig. 4. Histologic correlation of rosetted transplants and retinal detachment. Optical coherence tomograms (A and C), histology (B and D) of a rosetted multi-band (A and B), and single-band (C and D). The high reflection areas in the OCT image correspond to the rosetted areas in histology sections.

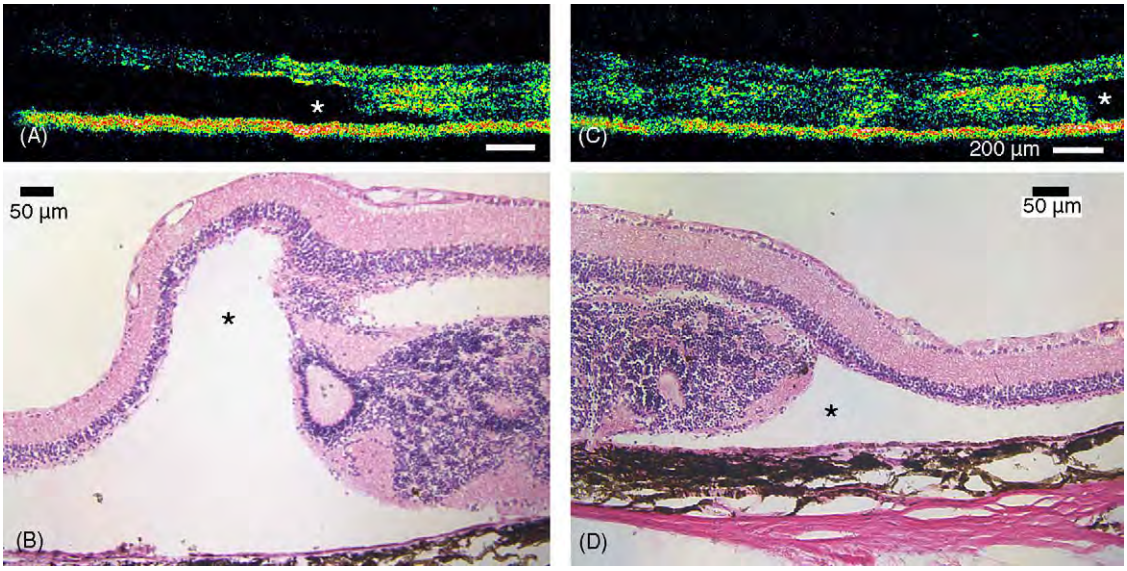

Fig. 5. Histologic correlation of retinal detachment. Optical coherence tomograms (A and C) and histology (B and D) of two grafts with retinal detachment (asterisk).

plantation surgery, were confirmed by gross examination and histologic evaluation (Fig. 5B and D).

4. Discussion

In this study, the correlation between OCT images and histology was investigated in transplanted and non-transplanted retinal degenerate S334ter-line-3 rats. OCT scan images could detect the presence of a subretinal graft in almost all the transplanted rats studied. There was only one single case, where a subretinal graft was missed by the OCT scan. On histologic evaluation, this graft was found to be extremely small in size. OCT evaluation was also able to reliably identify a misplaced graft. In some of our transplanted rats, the graft was placed in the choroid or epiretinal space, which could be easily identified during scanning.

OCT scanning can also be used as a technique to assist in identifying the non-laminated grafts containing mostly rosettes. In the present investigation, most of the eyes from the single-band transplant group (87%) showed poorly organized transplants that contained mostly rosettes with histology evaluation. In contrast to this, a considerable proportion of the eyes from the multi-band transplant group (47%) contained laminated areas in the graft when examined histologically. Formation of rosettes in the transplant can be the result of trauma occurring to the host RPE, and or due to the abnormal placement of the graft. The reason that OCT scanning could not detect the presence of laminated transplants in 53% of the rats may be because of the high incidence of rosette for-

mation. Even in the "best-laminated" transplant, laminated portions were restricted to a small region compared to a large area occupied by the rosettes. Also, some of the multi-band transplants on histologic evaluation showed partially laminated areas only in the interior layers (mostly bipolar cells) of the transplant, whereas the outer (photoreceptor) area mostly contained rosettes (Fig. 3C and D).

According to Gloesmann et al. (2003), the different intensity horizontal bands observed in the pig OCT image can be correlated with the various retinal layers. However, we were unable to demonstrate a similar correlation for the different bands observed in the OCT scan images of the transplants. This can be explained in terms of the higher resolution OCT instrument (ultrahigh-resolution OCT) used for the pig OCT study. It is possible that the bands observed in the OCT image of the transplants represents some of the intact retinal layers (inner plexiform, outer plexiform, inner nuclear, outer nuclear or outer segment layer) present in a laminated transplant. Considering the fact that in S334ter-line-3 rats, mostly well-laminated transplants resulted in restoration of visual responses in the superior colliculus (Sagdullaev et al., 2003), the OCT scanning technique can be an important tool for the qualitative evaluation of the retinal transplants.

This study also demonstrates that the OCT scanning technique is a reliable tool to measure the retinal thickness in rats. Reduced retinal thickness observed in OCT scan images of 21-day-old S334ter-line-3 rats is found to be well-correlated with histology data. Comparable observations have been reported in retinal degenerate (rd) mice (Horio et al., 2001; Li et al., 2001).

As a fast and reproducible procedure, OCT scanning can be used to monitor changes in the quality of the retinal transplants at different time periods after surgery. Interestingly, a reduced retinal thickness was observed among transplanted rats when scanning was performed at a later age after transplantation. This reduction in retinal thickness may be explained in terms of a better integration of the transplant with the host or due to the partial absorption of the transplant or host retinal tissue.

OCT scans are very sensitive in detecting retinal detachments. The reliability of OCT images to evaluate retinal detachments has been reported previously (Fukuchi et al., 2001; Li et al., 2001). Retinal detachment observed in some of our transplanted rats during OCT scanning was confirmed by gross examination and histologic evaluation. Thus, OCT may be a useful tool to evaluate for the presence of surgical complications, such as retinal detachments, which can influence the success of the treatment strategies.

In transplantation studies, animals are frequently followed for several weeks after surgery and subjected to various functional tests, including visual behavioral testing and brainstem electrophysiological evaluations. Some rats are also studied with trans-synaptic tracing techniques for the evaluation of the integration between the transplant and host. Transplanted eyes are then further processed for detailed histologic studies including electron microscopy. Unfortunately, these various evaluation procedures are generally only useful in eyes which contain well-organized (laminated) grafts in the subretinal space. As an in vivo screening procedure, OCT can increase the efficiency of the post-transplantation evaluation process, by screening out animals with poorly organized and defective transplants at an earlier age after retinal transplantation surgery. The technique may also be valuable for assessing retinal status following various other interventions in rodent eyes.

There are also other non-invasive techniques, such as fundus photography and scanning laser ophthalmoscopy (SLO) that are useful for fundus evaluation. Considering the fact that our transplants are transparent and the fundus photography is more time consuming, OCT may be a better choice, in the absence of more expensive equipment, such as SLO, for evaluating the retinal transplants.

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