Intraocular Retinal Transplantation: A Review

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SUMMARY

This review covers intraocular transplantation of retinal tissue. This has importance both for theoretical understanding of retinal and neural development and for possible future clinical application.

Transplantation sites have ranged from the anterior chamber through the retina to the subretinal space. Transplanted tissue has ranged from whole retina to specific retinal layers or specific types of retinal cells. Both within-species and inter-species transplants have been performed, and donor age has ranged from embryonic to adult. The ability of transplanted tissue to be accepted and to differentiate in host eyes has been studied. The conditions under which successful transplants are obtained, host-graft interactions, and transplantation methodologies have been explored. Morphological, and to a small extent, also functional characteristics of the transplants have been studied.

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INTRODUCTION

Studying retinal transplants is a way of obtaining insights into the development of retinal tissue and factors which influence this, the formation of neural connections, and interactions between transplanted and surrounding tissue. Additionally, there are many eye diseases which due to their effects on the retina cause severe visual loss. It is important to begin to preliminarily explore the possibility that transplantation techniques may be a means of replacing irreversibly damaged retinal tissue.

Studies of the development of retinal tissue when transplanted into host brains have been reported for some time /38,40-43/.

Apart from one pioneering study /46/, intraocular retinal transplants have been carried out only relatively recently. The sparse literature regarding retinal transplants up to mid-1986 has been reviewed /60/ and integrated into a review of retinal transplants into the brain, along with the use of peripheral nerve grafts

as bridges for the growth of retinal ganglion cells. A further review of retinal transplantation /11/ has also recently come to our attention.

The present review emphasizes recent developments in the transplantation of retinal tissue into host eyes.

TRANSPLANTS OF WHOLE RETINA

Transplants into the Anterior Chamber

Del Cerro et al. grafted retinas from Long-Evans rat embryos aged 13 to 16 postconceptual days (E13-E16) /14,15/ and 2 days post-natal (P2) /15/, to the anterior chambers of adults, both of the same species, and also of other species, namely Lewis /14, 15/ and Fischer /14/. The transplanted neural retina and the retinal pigment epithelium (RPE) grew at a roughly linear rate until one month after transplantation, after which its size and appearance remained unchanged. Iridal vessels entered the implants and formed branches with them. The capillaries within the implant formed tufts around the trunks of origin, in contrast to the vascular network found in normal rat retinas. Survival times (time from transplant till sacrifice) allowed in the study ranged from 0 to 90 days, with long-term survival rate for transplants larger than 1 mm ranging from 25% to 80%.

Fifteen days proved adequate for the differentiation of a rudimentary layered structure /14,15/. This included patches of outer (ONL) and inner (INL) nuclear layers (the INL sometimes forming a distinct layer), as well as definite inner limiting membranes (ILM) with baskets of Muller cell processes and outer limiting membranes (OLM) and outer plexiform layers (OPL). The plexiform layers contained numerous synaptic endings and both ribbon and conventional synaptic contacts /14,15/. (A ribbon synapse is characterized by a dense ribbon or bar seen in the electron micrograph of the presynaptic cytoplasm and always has multiple post-synaptic elements /23/. Conventional synaptic contacts in the retina are similar to those found throughout the vertebrate nervous system /23/. Both types of synapses would be expected to be found if the transplant resembles normal adult retinal tissue.) Photoreceptor outer segments, which were all stunted /14,15/, were only observed to develop when the pigment epithelium was present near, though not necessarily in contact with, the rod cells /14/. Rod cells were closely packed, and in some cases formed rosettes within the thickness of the ONL and INL /14,15/. Ganglion cells were present in transplants from embryonic /14,15/, but not from post-natal /15/ donors, and were few in number.

Within-species transplants were very well tolerated by the host, even 3 months post-transplantation /14,15/. Lewis strain hosts usually did not show inflammation /12,13/ while Fischer strain hosts showed an intense reaction /14/. This began in the form of vascular congestion of the iris, which could progress to general hyperemia of the conjunctiva, with clouding of the media. In the two worst cases, such alterations as anterior chamber hemorrhages, cataractous changes, along with vascularization and opacification of the cornea occurred. In these severe cases, the transplants were surrounded and infiltrated by macrophages, which were also plentiful in the host retina and were a major component of a granulomatous tissue found throughout the vitreal cavity.

Ninomiya /45/ transplanted retina from E13-E20 Fischer rats to the anterior chambers of adults, with survival times of 2-37 weeks. The transplanted tissue was seen as an irregular translucent whitish mass into which small blood vessels entered. Microscopically, tubular structures of varying sizes and some rosette-like structures were seen. Survival rate was 22%, but if a co-transplant of tectal tissue was made, then it was 74%. The retina-tectum double grafts fused about 2 weeks after transplantation.

Transplants to the Host Retina

Rat to rat transplants. Del Cerro et al. /12/ performed transplants from both embryonic and P1-P2 postnatal outbred Long-Evans rats into the retinas of adult male outbred Long-Evans rats and albino Lewis strain rats. The host retinas were either damaged prior to transplantation by light or by kainic acid or were normal. The transplant was either in the form of strips of retina or of a cell suspension. Survival times of up to 90 days were allowed. A mass of retinal tissue was found to develop on the host retina, and the nuclear and plexiform layers differentiated and were populated by the expected neuronal and glial types. Differentiation included the appearance of numerous rod cells, often forming rosettes, and a few cones. The

lumina of these rosettes were limited by an OLM and were filled by cilia-bearing inner segments and contorted outer segments. They also contained some macrophages loaded with cytoplasmic debris. The layers of the transplant came to blend with those of the host as they grew and became progressively vascularized. Synapses, both of the conventional and ribbon types, were found within the plexiform layer of the transplant /12/. In these types of transplant, and with survival times up to 120 days, no evidence of immune mediated rejection was found /13/.

In a similar study /20/, dissociated retinal cell suspension, in some cases prestained with either Fast blue or Fluoro-gold, was obtained from P1-P2 Long-Evans and Lewis pups. The cells were injected into the retinas of Long-Evans, Lewis and Fisher hosts (some phototoxically damaged). With survival times of 10, 30, and 100 days, the transplants showed excellent integration with the host tissue, without any glial barrier. In those cases which were not prelabelled, it was difficult to define precisely the distribution of the transplant in the normal host retinas. Precise transplant survival data were not given, but it was mentioned that in a few cases, viable grafts failed to occur /20/.

Further details regarding the results of transplantation of retinal cell suspensions to light-damaged host retinas have been reported for adult Fisher rat hosts with donors of the same species /17,19/. The photodamage had been achieved by 4 weeks of 12 hours per day of exposure to an illuminance of 3500 lux from fluorescent lamps. Transplants were from P2 donors, and were allowed to grow 3-100 days. They were found to grow well, although the laminar organization was less regular than in other transplantation methods /17,19/. Density of rod cell nuclei in the transplant was high (145 nuclei per 250 μm of retina), as compared to almost zero in light-damaged retinas without transplants (2.8 nuclei per 250 μm of retina), but it was approximately one-third of that found in the corresponding area of normal control retinas (415 nuclei per 250 μm of retina) /17/. Rod cells were usually grouped in rosettes /17,19/. Their inner segments developed consistently, while their outer segments tended to be defective, containing collections of irregular cisternae. Many synapses, both of the conventional and ribbon type, occurred within patches of plexiform layer around the grafts. Transplants could be found in approximately two-thirds of transplanted eyes.

Similar results were also obtained when transplants to photodamaged albino Lewis rats were performed, with donor material from P0 to P2 Lewis or Long-Evans rats /18/.

Turner and Blair obtained donor retinal tissue from newborn rat pups /56/. The retinas of the adult Sprague-Dawley hosts were lesioned by means of a razor blade that was passed through the layers of the eye until the vitreous was exposed, the incision being subsequently sutured closed. Donor retinas were cut into small pieces and injected into a host lesion site. The lesion either was newly prepared or 5 weeks old. Within 1 week post-transplantation, a distinct ganglion cell layer two or three cells thick was present, but without an optic fiber layer. There was a small inner plexiform layer (IPL) between the ganglion cell layer and the neuroblastic layer. At four weeks, an ILM and a continuous optic fiber layer were still absent. In some cases, however, fascicles of fibers ran from the graft ganglion cell layer and joined with and coursed for some distance along the host ILM/optic fiber layer. The neuroblastic layer had developed into an INL and an ONL separated by an OPL. Both ribbon and conventional synapses were present. Photoreceptor cell bodies and inner segments, but not outer segments, were found. The photoreceptors on occasion collected to form rosettes, with the cell bodies facing an inner luminal surface filled with microvilli. Merging of the plexiform layers of the graft and the host was observed. A clear distinction could be made between the host and graft tissue, the latter being located mostly within the cut edges of the lesion in the host retina. The transplants were successful for both fresh and 5-week-old lesion sites /56/ and also for 8-week-old lesion sites /59/. This last point, regarding lack of influence of lesion age on the success of the transplant, was also confirmed in a further study /4/.

Retinal transplants were performed by the same method, both from P1 pups and from E15 Sprague-Dawley embryos, into lesioned retinas of young adults of the same species /2,61/. Six to 7 weeks post-transplant, the P1 transplants had fewer laminae (only ganglion cell layer, IPL, INL and ONL) than the E15 transplants (OPL and OLM also present). The P1 transplants also integrated more poorly within the host retina under fresh lesion conditions, but equally well in

older lesions. For both donor ages, a continuous optic fiber layer and the ILM were again absent /2,61/. Glial cells from within embryonic grafts developed normally, while host glial cells also migrated into the grafts /49,61/. Graft filling and viability did not differ between newborn or embryonic donors /2,61/.

Retinal graft from E15 donors to a fresh lesion site also reduces the degeneration in the host retina in the region surrounding the lesion, compared to that which occurs with the lesion alone /32/. This effect is not specific for retinal grafts; similar results are obtained if sciatic nerve pieces are implanted, but not with implants of sheath tissue or tendon /57,58/.

An earlier study /4/ from the same laboratory involved using retinal donor material from P10 and P1 pups and E14-E20 embryos. The grafts were histologically examined when they reached the equivalent of age P28. They found that 10-day-old donor material resulted in a lower "evaluation index" (a quantitative measure of graft survival, lamination, integration with host retina, absence of non-neuronal barriers, and lesion filling and repair by the graft tissue) than that from 1-day-old donors. No significant difference in the "evaluation index" was found, however, between transplants from P1 pups and the embryos. The transplants from P10 donors had essentially no ganglion cell layer or IPL present. The cells from the INL were relatively few in number and quite disorganized. Massive fiber outputs which did leave younger grafts were absent from the P10 graft tissue. Photoreceptor cells dominated the cyto-architecture of these grafts in the absence of normal populations of other cell types. The average survival rate was over 90% /4/. As donor age increased from P2 to P21, the success of the transplant progressively declined. For P21 donors the transplant completely degenerated within 2 days, with no viable grafted tissue found in the lesion site /2,61/. Daily Cyclosporin A injections, however, allowed healthy retinal donor cells from 21-day-old donors to survive for at least 6 days /3/. If given only for the first 24 hours, only a remnant of the graft remained at 6 days, and it was infiltrated by connective tissue and some macrophages /3/.

It is interesting to note that integration even of donor retina frozen for several months to the temperature of liquid nitrogen is possible, although over a narrower range of donor ages /47/. The optimal donor age for transplants of strips of retina into lesioned host retinas is approximately E16. Donor age in excess of E19 leads to poorer success and differentiation, while E13 donor tissue rarely survives. Retinal tissue cryopreserved for 8 months survives and differentiates just as well as tissue cryopreserved for 4 months /47/.

Xenografts to rat hosts. Retinas transplanted from mouse embryos into retinal lesions of adult Sprague-Dawley rats required that the hosts be treated with daily Cyclosporin A (10 mg/kg) in order for the transplant to survive 30 days /3,61/. At 8 to 9 days post-transplantation, the grafts were still mostly undifferentiated and consisted of a neuroepithelial layer. By 30 days, the ONL, INL, IPL and ganglion cell layers were all identifiable within the rosette structures of the graft /3,61/.

In contrast to this result, strips of retina from newborn C57BL/6J mice transplanted into the posterior poles of Fisher 344 albino rats were still well accepted 17 days post-transplant without any immuno-suppression /8-10/. The transplants differentiated into ONL cells (with inner and outer segments attached to them), INL cells, and a plexiform layer. The reaction of the appearance of a few macrophages around the transplant was reported as being no worse than that found in corresponding intraspecies transplants /8-10/.

Strips of retina from a P60 and a P90 Cebus Appella monkey fetus transplanted into the eyes of adult Fisher 344 albino rats to which Cyclosporin A was administered were still not rejected 33 days post-transplant /16,31/. The graft differentiated into ONL cells with inner segments attached to them, INL cells, and a plexiform layer. It integrated well with the host retina and sometimes also expanded into the vitreal cavity /16,31/.

Non-rat hosts. The rabbit and the mouse are among the few species other than rats to have been utilized as intraocular whole retina transplant recipients.

Retinas from E15 albino rabbits have been transplanted to surgically lesioned retinas of 4- to 6-week-old albino rabbits /48/. At 4 weeks post-transplant, grafts of approximately 2 mm in diameter were found. Rosettes in the graft contained all retinal cell layers, with the exception of the ILM /48/. At 8 weeks post-transplant, the grafts appeared to be smaller and with fewer rosettes /1/. Transplanted

whole retina which included the RPE led to a higher success rate and usually larger graft sizes at 4 weeks post-transplant than whole retina without the RPE /1/.

Normal retinas from P0 mice were transplanted into adult mice with inherited retinal degeneration (rd/rd) /29/. Three days after the transplant, rosettes of grafted tissue showed photoreceptor differentiation. The survival rate for the transplants was high at 3 days post-transplant but dropped dramatically at 10-15 days, with a regressive change in the photoreceptors. Transplants from P0 (rd/rd) mice into normal mice, on the other hand, still had a good survival rate 10-15 days post-transplant, the grafts having numerous rosettes and some photoreceptors having well developed outer segments /29/. By 30 days the survival rate was reduced, but photoreceptors were still the majority of surviving cells /30/. The authors concluded that the retina or the intrinsic cellular defect itself may not be the only factors playing a role in this type of retinal degeneration /29,30/.

TRANSPLANTS OF SPECIFIC RETINAL COMPONENTS

So far in this review, whole retinal transplants have been discussed. Transplants of retinal components alone will now be considered.

Transplant of Separated Retinal Layers

Retinas from P4 Fisher rat donors have been separated into an outer layer consisting mainly of neuroblasts and an inner layer consisting primarily of ganglion cells, displaced amacrine cells, and astroglial elements /21,22,39/. Both layers of cells, when transplanted into both normal and light-damaged retinas of adult Fisher rats, successfully differentiated into photoreceptors, a plexiform layer, and a cell layer which was presumably the inner nuclear layer. Inner layer transplants survived better than outer layer transplants.

The intact photoreceptor matrix separated from the retinas of normal 7-day-old Sprague-Dawley rats has been transplanted to the subretinal space of photodamaged retinas of adult albino hosts of the same species /54/. Transplanted photoreceptors were found at survival times of 2, 4, and 6 weeks, with an overall success rate of 67%. The transplant remained approximately constant in size with survival time, and consisted of columnar stacks of about 12 cell bodies, which is characteristic of the photoreceptor layer, as well as some rosette formations. The number and length of photoreceptor outer segments was reduced, however /54/.

Photoreceptor layer transplants from adult human eyebank eyes to photodamaged adult host retinas were also successful, but only if the host rats were immunosuppressed /52/.

Retinal Pigment Epithelium (RPE) Transplants

The retinal layer which has most frequently been transplanted alone is the RPE. The earliest report of RPE transplant was from Gouras et al. They obtained human RPE cells from donors aged 65 to 85 years within 12 to 24 hours after death and cultured them *in vivo* /27/. Cells from the primary culture were subcultured and radiolabelled. The subcultured cells were transplanted to an area of Bruch's membrane of owl monkeys which had been exposed and denuded of host RPE cells. Survival times ranged from 2 hours to 7 days. Transplanted cells had already attached to the denuded area of Bruch's membrane at 2 hours and continued to divide thereafter. Leukocytes were observed in the choriocapillaris and Bruch's membrane at times as early as 2 hours. Macrophages appeared in the choriocapillaris and Bruch's membrane beginning at 3 days and increasing in number up to 7 days (immunosuppression was not used).

Lopez et al. performed transplants of cultured rabbit RPE cells from adult albino and pigmented rabbits to the subretinal space of normal adult pigmented rabbits /36/. Within an hour, cells attached to Bruch's membrane, and at 24 hours (the longest post-transplant time reported), some cells were phagocytosing receptor outer membranes. The success rate for the most successful method attempted was approximately 25%. The main problems encountered in their transplants were breaks in Bruch's membrane, unsuccessful denudation of the host pigment epithelium, and failure to inject a sufficient number of donor cells /36/.

When this type of transplant was followed for 6 months in non-immunosuppressed rabbits, there were granulomatous reactions with damage to the choriocapillaris and overlying photoreceptors /5/. Inflammatory cells traversed Bruch's membrane and entered the subretinal space. It was possible, however, to prevent these reactions, while also enabling transplanted RPE to survive the 6-month period by administering Cyclosporin /5/.

Li and Turner /34/ have transplanted cultured RPE cells from P6-P8 Long-Evans rat pups to Sprague-Dawley rat hosts of ages ranging from P10 to adult. Approach to the subretinal space was through the dorsal surface of the eye, without passing through the vitreous. Using survival times ranging from 2 hours to 3 months, the grafts were successful for all host ages attempted, with an overall success rate of 95%. The photoreceptors underlying the grafts remained normal.

An additional study describes pigment epithelium taken from the peripheral retina of 12- to 20-week-old Gottingen miniature pigs and transplanted to the subretinal space at the posterior pole of the same eye (autologous transplant) /33/. Cell attachment to Bruch's membrane was demonstrated 1 hour post-transplant. Efflux of cells to the vitreous and significant subretinal hemorrhage occurred in 40% of cases.

At least two laboratories have attempted to apply RPE transplantation to the prevention of the hereditary photoreceptor degeneration in the Royal College of Surgeons (RCS) rat, as will be discussed in the paragraphs which immediately follow. There is evidence that the gene for the retinal dystrophy in the RCS rat acts on the RPE cells /44/. Phagocytosis by RPE cells of photoreceptor outer segments, which is an important function of normal RPE cells, is deficient in the RCS rat /6/. Photoreceptor outer segments differentiate and elongate in a normal fashion until age P18; by P22, degeneration of photoreceptor cell nuclei is well underway, and photoreceptor degeneration is almost complete by P60 /24/. The implication of the RPE in this process (and the possibility that this may be a model for certain human retinal degenerations) has spurred the following studies.

Lopez et al. transplanted freshly harvested dissociated RPE cells from pigmented normal rats (of unspecified age; presumably adults) to the subretinal space of congenic RCS rats of age P15-P22 /37/. As long as 4 months post-transplant, areas in which transplanted RPE cells were present also had photoreceptor cells. The more donor RPE cells present in a region, the thicker was the host's photoreceptor cell layer in that region. Transplanted pigment epithelial cells contained many more phagosomes than normal /37/, while older cells /28/ had a higher content of older phagosomes than younger ones. Receptors survived even at a distance from transplants /28/.

Li and Turner transplanted RPE cells from black-eyed Long-Evans P6-P8 rats to the subretinal space of P26 non-pigmented RCS hosts with a 100% success rate /35/. When the hosts reached age 60 days, there was a retinal area of approximately 4.2 mm^2 where degeneration of host photoreceptors was prevented. Distinct zones of photoreceptor outer and inner segments were found, and the OPL was not reduced in thickness compared to its thickness at P26. In P60 nongrafted controls, however, the receptor outer segment membranes formed only a debris zone, while the inner segments had disappeared. The OPL was one-third of the thickness it had at 26 days /35/. Sheedlo et al. further found that the thickness of the ONL varied little in the region beneath a graft, even though the distribution of donor cells within the region of the transplant was typically random /50/. Starting at the transition zone between the graft and the host RPE, the ONL began to decrease in thickness. The distribution in retinal regions where photoreceptor degeneration was prevented of the membrane protein Na^+, K^+-ATPase and of the photoprotein Opsin was not different from that found in normal control Long-Evans rats. Both those transplanted RPE cells attached to Bruch's membrane and those on the apical surface of other RPE cells appeared to be able to ingest shed rod outer segments and membrane debris /50/. RPE transplants are able to prevent photoreceptor degeneration only if performed prior to the host age of approximately 30 days /51/. For transplants performed at P39, there was no significant photoreceptor cell rescue 3 months after grafting /51/.

While transplant of RPE alone does not effect photoreceptor rescue for RCS rat hosts older than P39 /51/, transplant of RPE together with dissociated photoreceptors to the subretinal space of 4- to 6-month-old hosts has been attempted /25,26/. Survival time of only 24 hours was reported, and photoreceptors were found in the subretinal space /25,26/.

While RPE transplants have been found to prevent photoreceptor degeneration in RCS rats, a third laboratory has found that surgical manipulation alone in P25 and P36 RCS rats, including injection of saline or implantation of a gelatin carrier without transplanted cells, is sufficient to prevent photoreceptor degeneration in the region of the surgery just as effectively /55/. Survival times of up to 2 months post-surgically were utilized /55/. The only one of the above-cited studies of RPE transplantation to RCS rats which included a sham control group /51/ (vehicle injected at 17 days) found only a partial and short-lived photoreceptor cell rescue. At age 2 months, the ONL was much thinner than with RPE transplant, and in a much smaller area, while at 3 months the rescue effect was no longer seen.

TRANSPLANT FUNCTION

In addition to observing the structural characteristics of transplanted retinal tissue, it is important to assess the extent to which the transplant functions like normal retina, and whether it successfully conveys visual information to higher centers. The sparse information on this subject which is available at the present early stage in the history and development of intraocular retinal transplantation is presented in this concluding section.

One study reports on the 2-deoxyglucose uptake in photoreceptors transplanted from P8 donors to adults with light-damaged retinas (they do not mention which animal) /53/. The uptake patterns in transplanted photoreceptor regions and underlying host INL, both under dark conditions and under 10 Hz flicker stimulus, were similar to that of normal retina.

Another study has been carried out on transplantation of retina from pigmented Westenberg Long-Evans rats to the anterior chamber of albino rats of the same species /7/. The response of the host retina to light, as measured by the electroretinogram (ERG), had been eliminated by poisoning with 6-hydroxydopamine. The ERG was detected in rats which received retinal transplants, while it was absent in those which received no transplant or a sham transplant of medium only.

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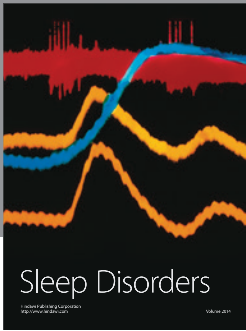

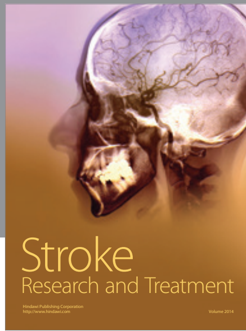

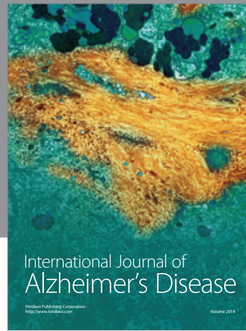

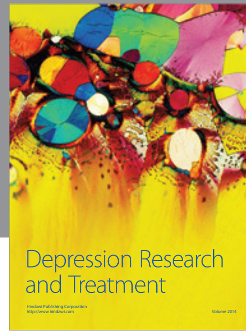

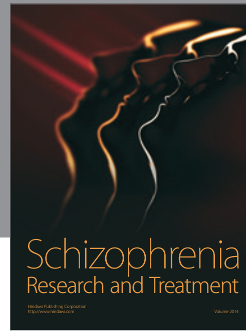

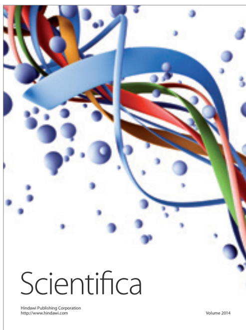

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