Animal Models of Retinal Injury

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Retinal injury is a common cause of profound and intractable loss of vision. Clinical outcomes are poor in both open and closed globe injuries because cell death, scarring, and a failure of tissue and axon regeneration are not ameliorated by current treatments. Much animal research is directed at understanding and modifying these pathologies, although results have yet to translate into clinical practice. Axotomy-induced retinal ganglion cell (RGC) death in mammals can be effectively reduced and axon regeneration enhanced over the short term. After retinal injury in mammals, the retinal pigment epithelium (RPE) and retinal glia either regenerate lost RPE and neuroretinal cells or form nonfunctional scars. An understanding of the mechanisms underlying injury responses is critical to the successful development of therapeutic strategies to promote ocular repair. (*Invest Ophthalmol Vis Sci.* 2012;53:2913–2920) DOI:10.1167/iovs.11-8564

Ocular trauma has a lifetime prevalence of 19.8% in civilians and up to 1% involve retinal injury.[1,2] Young males, manual workers, and the military are at particular risk.[1] Up to 13% of soldiers wounded in action suffer eye injuries, 80% of ocular war injuries are related to explosive blast, and 60% have concomitant retinal injuries.[3,4] Retinal injury is the most common cause of profound and intractable posttraumatic visual loss, with poor outcomes due to retinal cell death, scarring, and a failure of functional regeneration.[3] Notwithstanding much animal research aimed at both understanding the mechanisms underlying these three processes and developing potential treatments, current surgical practice often fails in all three areas. In this review, we aim to provide an overview of the different animal models used to study retinal trauma, to facilitate future translational research choices in this important area. We separate closed from open globe injuries,[3,4] which are considered in the context of proliferative vitreoretinopathy, optic nerve injury and axon regeneration, neurosensory retinal regeneration, and retinal pigment epithelium (RPE) repair and regeneration.

Comparative Anatomy of the Eye

The eyes of different mammals vary in size, refractive properties, retinal vasculature, and visual photopigments (Table 1), although the retinal cellular composition and thickness are conserved (0.24 mm thick in the mouse and in humans).[5] Mammalian rod photoreceptors are similar: all contain rhodopsin, but size varies by animal size and diurnal/nocturnal behaviors, with peak rod densities of over 400,000/mm^2, the nocturnal bush baby to 180,000/mm^2 in the diurnal rhesus monkey.[6] The proportion of cones and their function is highly variable with two classes—short (blue/UV) and medium (green) wavelength—of opsin pigments in mice, rats, rabbits, pigs, and most New World primates and three classes of cone (allowing trichromatic color vision) in Old World monkeys and great apes.[7] Murine rodents have cones distributed throughout the retina, with dorsal–ventral differences,[8,9] whereas in rabbits and pigs cones are concentrated in a "visual streak" and in diurnal primates at a fovea.[6,10,11]

Albino rats are commonly used in research, but have nonpigmented RPE, abnormal decussation of retinal ganglion cell (RGC) axons at the optic chiasm, reduced visual acuity, and a high susceptibility to light-induced photoreceptor apoptosis.[15] Most of the blood supply of the (merangiotic) rabbit inner retina is derived from the choriocapillaris but, in (holangiotic) human, primate, pig, and murine rodent inner retinae is from central and cilioretinal arteries; only the outer retina is supplied by the choriocapillaris. In the rabbit retina, RPE is irregular in size and arrangement compared with the human regular hexagonal configuration, the rods and cones are longer and thinner and myelinated nerve fibers in the retina form nasal and temporal crescents about the optic disc.[13] These differences limit comparisons of albino rat and rabbit models with human injuries.

Closed Globe Injury

Commotio Retinae

Commotio retinae describes gray–white opacification of the neuroretina after blunt ocular trauma, which resolves over days to months. Visual loss (when the macula is affected) may be transient or permanent.[16] It has been induced using either a modified airgun or a catapult in various species (Table 2). A larger projectile gives a lower area-normalized impact energy, which predicts injury better than total impact energy, explaining the high energy reported by Hui et al.[17] (Table 2).[18]

Some studies used central corneal trauma,[17,19–21] whereas others used lateral scleral injury.[21–23] Central corneal impact (1.3 J) to enucleated pigs eyes reduces axial length by 40%, causing corneolenticular contact and leaving approximately 3.5 mm between the retina and posterior lens surface.[24] In a lateral scleral impact, the retina will contact the centrally positioned lens. Despite this, ultrastructural findings are the same with both methods.

Electron microscopy demonstrates traumatic disruption of the photoreceptor outer segments,[19,20,22] and intracellular edema of Müller cell processes and axons consistent with optical coherence tomography findings in humans.[22,25] The damaged outer segments are phagocytosed by the RPE, which becomes multilayered.[19] There is conflicting evidence about blood retinal barrier disruption from porcine, feline, lapine, primate, and human studies. A normal fluorescein angiogram has been reported,[19,26] but indocyanine green angiography shows choroidal damage and horseradish peroxidase and lanthanum detect leakage across the RPE[17,20,23,26] (Table 2). Regeneration of photoreceptor outer segments occurs from 1 week to 2 months.[20,22] Nuclear pyknosis

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Table 1. Summary of Comparative Anatomy

Species	Axial Length, mm	Lens Size, % of Axial Length	Peak Rod Density, Cells/mm²	Cones, %
Mouse	3.4[5]	60[5]	437,000[12]	3[9]
Rat (Fig. 1)	6.3[5]	60[5]	400,000*	1[8]
Rabbit (Fig. 2)	16–19[13]	43[13]	300,000[10]	5[10]
Pig (Fig. 3)	23.9[14]	31[14]	113,000[11]	12.5[11]

* Unpublished data (Blanch RJ).

indicates photoreceptor death,[19] although its mechanism, or that of outer segment regeneration, has not been reported.

Blast Injury

Primary blast injury (PBI) is directly caused by an explosive blast shockwave, secondary blast injury by fragments carried by the blast wind, and tertiary blast injury by the blast wind itself. An explosive shockwave is a hypersonic energy wavefront from the transient overpressure of the explosion that causes energy transfer at tissue interfaces.[30] PBI affecting the gas-filled organs (lungs, ears, gastrointestinal system) are well recognized, ocular PBI less so.[30] Reports of ocular PBI from rat RGC axon degeneration after a simulated blast in a "shock tube" and rabbit RGC apoptosis after exposure to firecrackers did not control for tertiary blast injury.[31,32]

Open Globe Injury

Proliferative Vitreoretinopathy

Most animal models of open globe retinal injury involve penetrating injuries with vitreous loss, managed conservatively. This promotes a form of intraocular fibrosis, termed proliferative vitreoretinopathy (PVR), which is the endpoint of a number of traumatic processes, including surgical repair of retinal detachments. Of 27 existing models of PVR, 4 are from posterior segment trauma.[33,34] PVR with retinal injury has been created in rhesus monkeys, pigs, rabbits, and mice by penetrating the posterior chamber with or without lens extraction and reinjection of homogenized lens or blood and mechanical or thermal retinal damage.[33–35] In these models, multilayered RPE-derived fibroblasts are observed after 1 week and tractional retinal detachment by 2 weeks.[34,36] It is prevented by complete vitrectomy within 14 days, matrix metalloproteinase 2, 3, and 9 inhibition, or by x-ray irradiation.[34,37,38]

Retinal Response to Injury

RGC Death and Axon Regeneration. The RGC response to injury is most studied: isolated RGC pathology is produced by optic nerve injury, a closed globe injury; however, it is combined with surgical interventions (i.e., open globe injury) that manipulate cell death and regeneration. The molecular mechanisms underlying these processes are conserved throughout the CNS and retina. Traumatic optic neuropathy occurs in up to 20% of military ocular trauma,[4] and often causes profound and intractable visual loss. The optic nerve is a simple and accessible CNS tract in which to study the response of RGC to injury, and model CNS injury in general (Table 3).[55–57] After intraorbital axotomy RGCs display transitory axonal sprouting, then approximately 90% apoptotic death by 14 days.[40] To restore functional vision to patients with optic neuropathy, RGC death must be prevented and axon regeneration enhanced.

In rats, axotomy caused by optic nerve transection or proximal injury causes a more aggressive pattern of RGC death than optic nerve crush or distal injury, with differing transcriptional responses and neurotrophic factor efficacy.[40,58] Therapeutic interventions include recombinant neurotrophins, small molecule inhibitors, siRNA silencing proapoptotic or growth inhibiting genes, and viral vectors encoding therapeutic molecules or delivering shRNA, all of which are most easily administered by intravitreal injection.

RGC Apoptosis. Apoptosis (regulated, physiological programmed cell death) is distinct from necrosis (uncontrolled cell death by lysis with inflammation). After axotomy RGC apoptosis is triggered primarily by the activation of caspase proteins. Initiators such as caspase 8, 9, and 10 activate effectors such as caspase 3, 6, and 7 to cleave key cellular components and activate other

Table 2. Animal Models of Closed Globe Retinal Injury

Animal	Impact Site	Energy, J	Velocity, m/s	Weight, g	Injuries Reported
Pig[21,22]	Nasal sclera over ora serrata	0.49–1.8	50–64	0.38	Retinal breaks, choroidal rupture, and RPE disruption at lower energy. Commotio retinae at >0.68 J. Gross retinal disruption 1.8 J.
Pig[23]	Lateral sclera over pars plana	0.32	33	0.57	Commotio retinae, vitreous hemorrhage, no breaks/dialyses.
Owl monkey[19]	Central cornea	**0.39–1.05**	47	**0.35–0.95**	Commotio retinae only.
Cat[20]	Central cornea	**0.44**	50	0.35	Commotio retinae, variable hyphema.
Rabbit[28,29]	Lateral sclera over retina	0.57–1.62	**46.8**–79	0.52	Retinal tears and necrosis, choroidal and vitreous hemorrhage. Commotio retinae at lower energy, rupture at higher energy.
Pig[21]	Central cornea	0.49–1.9	50–100	0.38	No injury at low energy. Dialysis in 50% at higher energy.
Pig[27]	Paracentral cornea	1.25	52.3	0.95	Commotio retinae, RPE disruption, RPE and retinal detachment.
Rabbit[17]	Central cornea	2.87	**18.9**	16	Commotio retinae only.

Bold figures are calculated/estimated from published data.

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Table 3. Animal Models Used to Study Open Globe Injury Responses

Injury	Animal	Cells Affected	Response Studied	Technical Details
Incisional retinal injury[39]	Rat/mouse	Cells of all retinal layers near the wound	Cell death	Incision through sclera, choroid, and retina, <1 mm in length, closed with sutures.
Optic nerve crush[40]	Rat/mouse	RGC	RGC apoptosis and axon regeneration	Proximal injury (0.5 mm from globe) causes more aggressive cell death than distal (>8 mm).
Optic nerve transection[40]	Rat/mouse	RGC	RGC apoptosis	
Retinal detachment[41–46]	Pig/cat/rat/mouse	Photoreceptors	Apoptosis, programmed necrosis, "deconstruction"	Detachment is created by subretinal injection of balanced salt solution or hyaluronic acid (prevents reattachment) with/without vitrectomy and lensectomy. The cannula is introduced into the eye through a small pars plana/peripheral retinal sclerotomy and the subretinal space at another site.
		Bipolar, horizontal, ganglion cells	Remodeling, neurite outgrowth	
		Müller glia, astrocytes	Gliosis	
	Rabbit	Photoreceptors, glia	Aggressive cell death, gliosis	
Intravenous sodium iodate[47]	Pig/rabbit/rat/mouse	RPE	Cell death and tissue regeneration	>10 mg/kg is toxic in rats.
Intraperitoneal N-methyl-N-nitrosourea[48,49]		Photoreceptors		>15 mg/kg is toxic in mice; 60 mg/kg obliterates the outer nuclear layer.
Intravitreal N methyl-D-aspartate[50]		RGC, amacrine cells		Dose-dependent loss of neurons but wide variation in dosing.
Mechanical RPE debridement[51–54]	Primate/pig/cat/rabbit	RPE	Tissue regeneration and scarring	A vitrectomy is performed through a pars plana incision and a retinal detachment created by a subretinal balanced salt solution injection to expose RPE. Mechanical debridement is by abrasion with a silicone brush or tubing or tearing with forceps.
Hydraulic RPE debridement[51]				

degradative enzymes. Transient broad spectrum caspase inhibition by AAV (adeno-associated virus)-transduced p35 overexpression results in sustained RGC survival.[59] AAV-transduced Bcl-X_L overexpression opposes mitochondrial initiation of apoptosis (via caspase 9) and is highly neuroprotective.[60] The executioner caspase for RGC is disputed; activated caspase 2 and 3 have been shown by immunohistochemistry and Western blotting and inhibition of caspase 2, 3, or 6 increases RGC survival.[61,62] The most effective neuroprotection is by siRNA knockdown of caspase 2 (almost 100%).[61]

Upstream of the caspase pathways, a number of neurotrophic factors, including brain-derived neurotrophic factor (BDNF), ciliary neurotropic factor (CNTF), glial cell–derived neurotrophic factor (GDNF), neurturin, neurotrophin-4/5 (NT-4/5), erythropoietin, and inosine, protect RGC from apoptosis after axotomy.[57,63] BDNF downregulates its tyrosine kinase receptor (Trk) B, providing temporary neuroprotection, which is prolonged by AAV-transduced TrkB overexpression.[64] BDNF and CNTF act through PI-3-kinase/Akt/mTOR (phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin) and MEK/ERK (mitogen-activated protein kinase/extracellular signal related kinase Trk).[65,66] CNTF also acts through the JAK/STAT (Janus kinase/signal transducers and activators of transcription) pathway.[66]

RGC Axon Regeneration. Many prosurvival neurotrophic factors are also axogenic, but the underlying signaling mechanisms are distinct.[67] Glia have a prominent paradoxical role in either supporting or blocking axon regeneration. Activated glia in the retina and optic nerve produce multiple proregenerative neurotrophic factors.[67,68] However, reactive astrocytes in the optic nerve produce a glial scar, which contains proteoglycans that inhibit axon regeneration.[69] Nogo, a myelin-derived and Müller glial protein, and other myelin-derived inhibitors inhibit axon growth, acting through the Nogo-66 receptors to modulate GTPase Rho A and its downstream effector Rho-associated, coiled-coil containing protein kinase 1 (ROCK), and/or intracellular calcium levels.[56,57,70] Transfection with a dominant negative Nogo receptor enhances RGC axon regeneration, but only when combined with an activated growth state.[71]

PTEN (phosphatase and tensin homolog), SOCS3 (suppressor of cytokine signaling), and TSC1 (tuberous sclerosis complex 1) negatively regulate the mTOR pathway, and their deletion or conditional knockout stimulates, whereas administration of the mTOR inhibitor rapamycin reduces RGC survival and axon regeneration.[72,73]

Inflammation. Axotomy-induced RGC death and incisional injury-induced death of other retinal cells are reduced and RGC axon regeneration induced by various proinflammatory stimuli, including lens injury, intravitreal injection of zymosan (macrophage activator/chemoattractant), and intravitreal peripheral nerve grafting,[56,57] although not by retinal injury alone or tendon and nerve sheath implants, which also cause inflammation.[39,56] Schwann cells in peripheral nerve grafts secrete gp130 cytokines (e.g., CTNF or leukemia inhibitory factor), which may contribute to their neurotrophic effects.[56,74] After lens injury and intravitreal zymosan injection, retinal astrocytes and Müller cells release CNTF and are essential for axon regeneration.[67,68]

Activated macrophages enhance the neurotrophic effects of peripheral nerve and lens tissue.[56,57] Macrophages have multiple phenotypes and functions: "M2" type are proregenerative, whereas "M1" are neurotoxic.[75] Thus, macrophage stimulation may reduce and inhibition enhance RGC survival.[76] Macrophages release the calcium binding protein oncomodulin, which acts through intracellular mammalian sterile 20-like kinase-3b (Mst3b) and, dependent on high levels of cAMP, mediates their neuroprotective and regenerative effects,[77] which are also partially dependent on the axon guidance molecule EphB3.[78]

The JAK/STAT, MEK/ERK, and the PI3-kinase/Akt/mTOR intracellular signaling pathways are all important mediators of neuroprotection. Inhibition of these pathways may be proapoptotic and growth inhibitory or it can be neuroprotective and proregenerative, dependent on activated macrophages for JAK/

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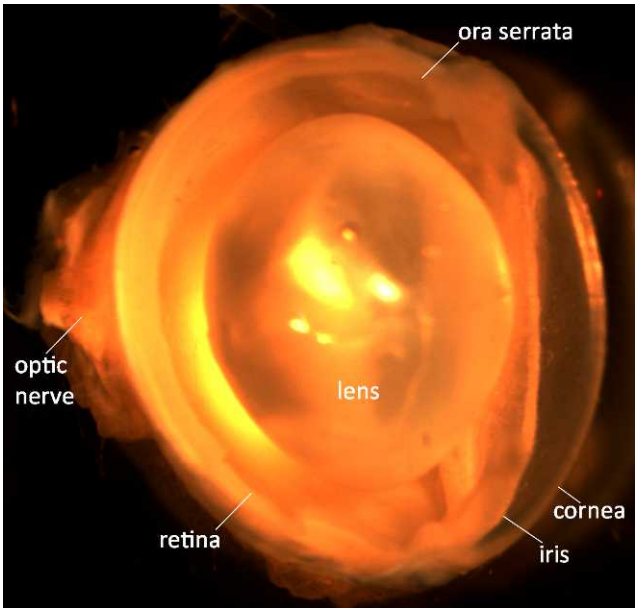


Figure 1. Labeled cross-section of the eye of an adult Wistar rat.

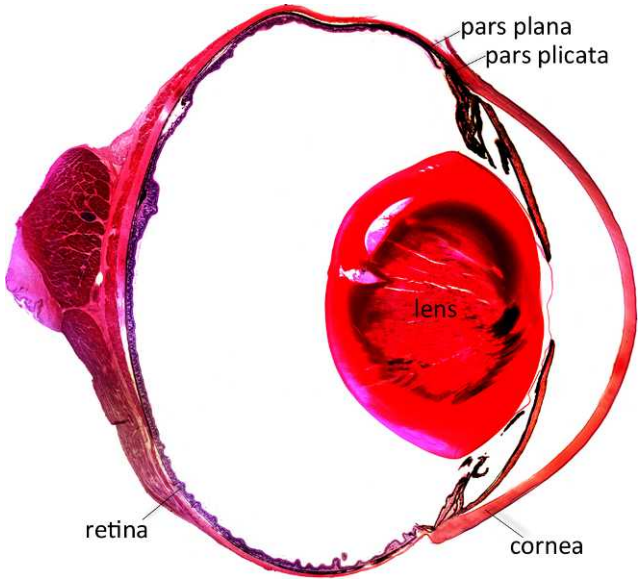


Figure 2. Labeled cross-section of an adult rabbit eye.

STAT and PI-3 kinase/Akt/mTOR and independent of them for MEK/ERK.[66,79]

The longest reported distance for RGC axon regeneration, with occasional axons reaching the thalamus, was induced by PTEN deletion, elevated cAMP, and activated macrophages.[80] The underlying mechanisms of RGC axon regeneration in the peripheral nerve graft and lens injury models remain controversial.

Retinal Cell Death and Remodeling

Animal models of open globe injury used to study retinal cell death and tissue regeneration damage the retina by incision, excision, or abrasion (Table 3).

Death of non-RGC retinal components has been little studied in models of trauma. Photoreceptor apoptosis occurs in closed globe injury and cells of all retinal layers die adjacent to penetrating wounds (Table 3).[19,39] Within hours of penetrating injury and retinal detachment in rats, fibroblast growth factor receptor (FGFR1) is upregulated in photoreceptors and fibroblast growth factor 2 (FGF-2), CNTF, and pigment epithelial-derived factor (PEDF) are released.[81–83] FGF and CNTF reduce photoreceptor apoptosis in other models of photoreceptor degeneration.[55]

Retinal detachment, usually created by subretinal hyaluronic acid infusion, models components of the injury response (outer retinal damage and ischemia; Table 3). Reattachment can be achieved by fluid–gas exchange.[41]

Photoreceptor outer segments are disrupted by detachment and in most models 20% die after 3 days, up to 50% with longstanding detachment. In the rabbit retina, all photoreceptors die, as do cells of the inner retina. After retinal detachment 60% of photoreceptors die by apoptosis, the remainder by programmed necrosis dependent on receptor interacting protein (RIP) kinases.[84] Intrinsic pathway inhibition, by AAV-transduced X-linked inhibitor of apoptosis overexpression or heat shock protein (HSP70) downregulation of the mTOR pathway and extrinsic pathway inhibition by Fas receptor blockage partially protect photoreceptors, as does apoptosis inducing factor-deficiency.[44,45,85,86] Thus all regulated cell death pathways are implicated, but complete photoreceptor protection has not yet been achieved.

The retinal response to detachment involves significant remodeling. Photoreceptor outer segments shorten within days (deconstruction) and mitochondria redistribute from the inner segments to the cell body.[41] Rods show RhoA-dependent retraction of their axons from the outer plexiform layer (OPL) but continue to synthesize outer segment proteins.[42] Cone synapses remain in the OPL but, by 7 days of detachment, cone-specific protein expression is immunohistochemically undetectable.[41] Rod bipolar cells remodel leaving fewer dendrites, some innervating retracted rod synapses in the outer nuclear layer.[41]

Horizontal cells and RGC extend neurites throughout the retina and into the subretinal space.[41] RPE cells proliferate and migrate in the subretinal space or onto the inner retinal surface.[41] Müller glia proliferate, positively regulated by the mTOR pathway, and upregulate intermediate filament proteins, including GFAP, vimentin,

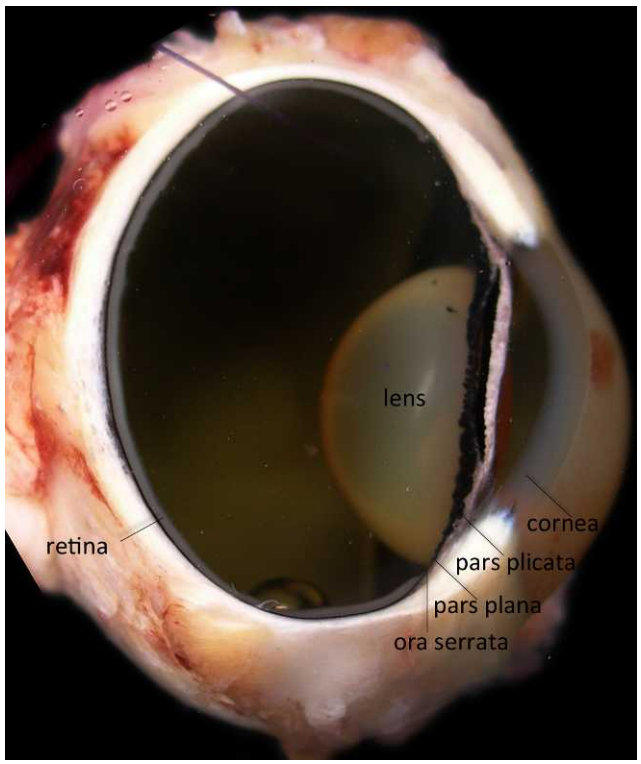


Figure 3. Labeled cross-section of the eye of an adult Large White pig.

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nestin, and synemin, thicken, extend processes, and migrate through the retina, into the subretinal space, along the epiretinal surface, and (after reattachment) into the vitreous to form gliotic scars.[43,46,87] Astrocytes also proliferate and, along with Müller and RPE cells and RGC and horizontal cell neurites, are found in epiretinal membranes after reattachment.[41] Gliotic scarring is also the dominant response to incisional retinal injury.[88] Upregulation of the cell cycle–related transcription factors c-fos and jun-B occurs within 30 minutes of injury and GFAP and PCNA are upregulated by 3 days.[89–91]

Retinal function after reattachment is reduced by altered synaptic connectivity, photoreceptor apoptosis, and imperfect outer segment regeneration (especially cones), which is further impaired by subretinal scarring.[41]

Retinal Tissue Regeneration

RGC axons and retinal tissue regenerate in adult zebrafish (*Danio rerio*), and this has been extensively studied in retinal excision, light injury, chemotoxicity, heat injury, and transgenic photoreceptor degeneration models.[92] A peripheral population of stem cells at the ciliary margin continually generates new cells of all retinal layers except rods, which are generated from stem cells in the outer nuclear layer.[92] After injury, Müller glia dedifferentiate into multipotent progenitor cells and replenish the different cell populations including rods.[92]

In embryonic chick and rat, excised retina regenerates from RPE.[93] However, the adult mammalian retina has low regenerative potential. After chemical injury to the murine retina, a small number of Müller glia migate through the retina and enter the cell cycle expressing the progenitor cell markers, nestin, proliferating cell nuclear antigen (PCNA), and Pax6.[48,50] Differentiation into photoreceptors is enhanced by exogenous BDNF, bipolar cells by retinoic acid, and amacrine cells by either epidermal growth factor (EGF) or FGF-1 combined with insulin.[48,49] Tissue regeneration is opposed by transforming growth factor β.[94] This glial dedifferentiation occurs through cyclin D1- and D3-related pathways, positively regulated by the Notch and Wnt (wingless-type MMTV integration site family) 3a/β-catenin protein signaling pathways.[48,50] Reelin may attract and direct stem cells.[95]

Thus, after injury, mammalian glia form scars and block the growth of regenerating axons, whereas zebrafish glia regenerate lost retinal tissue by generating new neurons. There is a limited potential for mammalian glia to regenerate lost tissue and this can be enhanced by exogenous neurotrophins.

Retinal Pigment Epithelium Regeneration

RPE injury is modeled by hydraulic or mechanical RPE debridement (Table 3).[51–53] The overlying neuroretina may be excised or left intact.[51,52] Chemical RPE debridement has been established by subretinal or (most commonly) intravenous sodium iodate and injures central more than peripheral RPE[47,96] (Zhou Z, et al. *IOVS* 2002;43:E-Abstract 3445). Hydraulic and chemical RPE debridement leave Bruch's membrane intact; however, other injury methods damage Bruch's membrane and the choriocapillaris.[51,53]

RPE cells surrounding the denuded Bruch's membrane lose their polygonal shape and polarity and migrate to cover the defect by 4 days, with or without overlying neuroretina, and may form a pigmented monolayer when the neuroretina is present.[97] They become hypopigmented and remain so after 9 months.[53] Disorganized RPE multilayering and replacement by fibroblasts occurs to a variable extent.[51,97]

Raising a retinal detachment shears photoreceptor outer segments, which regenerate in the presence of RPE,[98] although some photoreceptors die.[99] Damage to Bruch's membrane or subretinal mitomycin-C prevent RPE resurfacing, causing the outer retina and choriocapillaris to degenerate.[99]

RPE excision or damage stimulates local cellular proliferation in rabbits and monkeys[97,100] and peripheral RPE proliferation in pigs and rats,[54,101] enhanced by subretinal amniotic membrane grafting or intravitreal FGF-2 injections.[54,102] In adult rats, peripheral RPE shows greater recovery than central RPE after sodium iodate toxicity,[96] and there is a small peripheral population of dividing RPE cells (10–15 cells per eye), which could represent a pool of peripheral progenitor cells.[103]

Summary of Models

Species Considerations

The choice of species for animal modeling of human diseases is based on considerations of comparative anatomy, availability, and the body of previous work, which allows comparison.

Comparison of the merangiotic rabbit retina with human inner retinal injury responses is tenuous. The small size, ease of husbandry and genetic manipulations, ready availability of antibodies for molecular studies, and similarities in retinal cellular and vascular structure to humans make murine rodents very attractive models of ocular trauma. Albinos are less suitable than pigmented rat strains for RPE, photoreceptor, and functional/behavioral studies. Larger animals such as pigs and primates have anatomy comparable to that of humans and few scientific disadvantages. Their use is limited by capital costs, husbandry, and ethical issues.

Cell Death and Regeneration in Closed Globe Injury

Closed globe injury is achieved by moderate velocity impact, most commonly to sclera. A murine model would be ideal, but, of those reported, pig and primate models are the most suitable for translational studies.

Axotomy-Induced RGC Death and Axon Regeneration

RGC death and axon regeneration are most commonly studied in murine models. Optic nerve transection causes the most aggressive cell death, although optic nerve crush leaves greater potential for axon regeneration. To stimulate axon regeneration, mTOR activation, and/or a combination of activated macrophages with other stimulatory factors, such as lens injury and intravitreal peripheral nerve grafting, are most effective.

Neuroretinal Cell Death and Regeneration in Open Globe Injury

Rats and mice are suitable for open globe injury modeling, but when macular architecture is needed, primates are required. Cone injury responses may be studied more effectively in rodents because cones are distributed throughout the retina.

Transscleral penetrating injuries release neurotrophins, causing PVR. Smaller wounds through the pars plana or anterior chamber reduce the risk of PVR and allow more defined retinal injuries, such as injuring retina but not RPE.

RPE Repair and Regeneration

RPE injury is studied in rabbits, cats, and pigs by RPE excision through a pars plana wound using either hydraulic debridement (which preserves Bruch's membrane and the choriocapillaris, facilitating RPE resurfacing) or debridement with silicone tubing or forceps (which damages Bruch's membrane and the choriocapillaris, impairing RPE resurfacing). Preserving the overlying neuroretina by injuring RPE under an induced retinal detachment also affects healing.

Conclusions

RGC survival and long distance axon regeneration has been induced after axotomy, but regeneration is not functional and

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regenerative mechanisms have yet to be fully defined and clinically exploited. The mammalian retina and RPE can regenerate lost tissue from progenitor cells. However, neither the cell death mechanisms in cells other than RGC nor strategies to enhance tissue regeneration after open or closed globe trauma have been extensively studied. Protection and induced regeneration of these tissues is an achievable goal requiring suitable animal models, such as those described here.

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