CHAPTER 71

Retinal detachment

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Clinical background

Retinal detachment (RD) is a physical separation of the neural retina from the retinal pigmented epithelium (RPE). An important physiological ramification of the creation of a detachment is an increase in the physical distance between the photoreceptor cells and their blood supply, the choroicapillaris. Detachment recreates a space that disappears during early embryonic development.

Definitions: types of retinal detachment

Detachment occurs in three categories: exudative (or serous), traction, and rhegmatogenous (Box 71.1).

Serous detachment

Serous detachment occurs as fluid accumulates between the neural retina and RPE, but the retina remains physically intact.[1] Serous detachments may be idiopathic or occur as part of inflammatory reaction, or as a result of neoplastic ocular tumors (Box 71.2).

Tractional detachment

Tractional detachment occurs as a result of "vitreoretinal adhesions" or the growth of cells in the vitreous that attach to the surface of the retina and contract, mechanically creating an RD.

Rhegmatogenous detachment

This is the commonest form of RD and the focus of this chapter. It results from a tear across the retina, creating a physical continuity between the vitreous and RPE–photoreceptor interface and thus resulting in the accumulation of "foreign" fluid beneath the retina and a subsequent detachment (Figure 71.1).

Tractional detachments can also be rhegmatogenous, i.e., a complex form of RD (Figure 71.2).[2] These often result from fibrotic or scar tissue that forms on either surface of the retina after reattachment. Contraction of this scar tissue can cause traction on the retina with wrinkling and redetachment and often retearing of a previous break or creation of new ones. This is a visually devastating condition and its prevalence has remained discouragingly static over the years.

Symptoms, signs of retinal detachment, and diagnostics

All RDs are accompanied by some loss of visual function but this will vary depending upon the type of detachment, its size, and retinal location, making it difficult to ascribe one set of symptoms to the condition (Box 71.3). Diagnosing RD is complex with many qualifications.

Abnormal vision is the only reliable symptom of RD. But the types of abnormal vision are large and varied: light flashes, floaters, changes in the peripheral visual field, decreased acuity, defective color vision, distorted vision (metamorphopsia), or even unilateral double vision (diplopia). Patients often remain unaware of large peripheral detachments until they approach the macula and begin to produce a visual field defect. Many times they are discovered during an ocular examination. Foveal detachment always involves loss of central visual acuity. Indeed, the duration of a foveal rhegmatogenous RD is based upon the time of patient-observed decrease in visual acuity.[3] A macular rhegmatogenous RD will generally produce visual acuity loss that cannot be corrected, while blurred vision produced by a centrally located serous detachment (central serous retinopathy, or CSR) can often be corrected by shifting the focal plane of the image to a more forward location. The book series *Retina* includes much information relevant to diagnosing detachments.[4]

History

Greg Joseph Beer provided what is generally described as the earliest description of detachment in the early 18th century[3,5]; his observations were done without benefit of an ophthalmoscope (an instrument with magnifying lenses that allows examination of the inside of the eye). After Hermann von Helmholtz recognized the importance of the ophthalmoscope in about 1850, detailed descriptions of detachments and accompanying breaks or tears proliferated rapidly.

The first treatment of rhegmatogenous RD by sealing the retinal break with a red-hot probe occurred in 1889, and was revived as a standard treatment by Jules Gonin. Gonin was also the first to suggest a relationship between detachment duration and successful visual recovery. His technique is

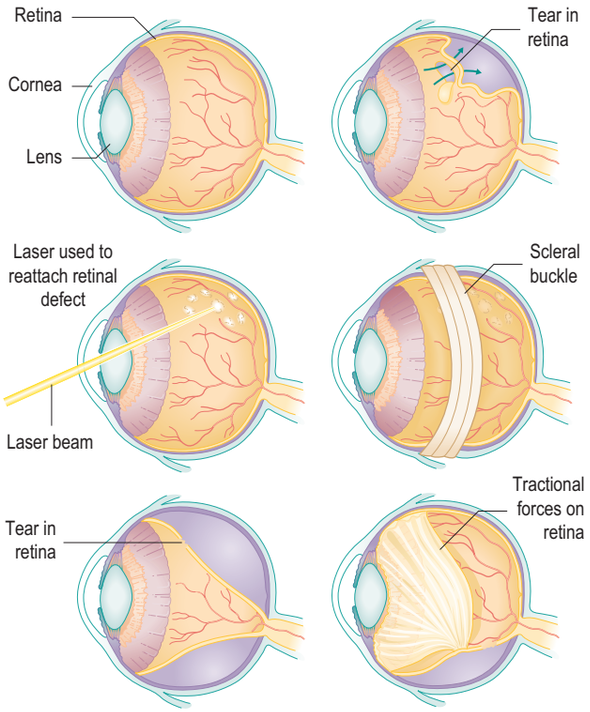

Figure 71.1 In a rhegmatogenous detachment a tear or break forms in the retina, allowing fluid from the vitreous cavity to enter, and creating a space between the neural retina and retinal pigmented epithelium (RPE). A laser can be used to "seal" the retinal tear and encircling bands of material (scleral buckle) can be used to indent the wall of the eye so that the retina is reapposed to RPE. Natural adhesion forces will allow reattachment to occur. A rhegmatogenous detachment may detach the whole retina. A serious complication of reattachment is the formation and attachment of scar tissue on the vitreal surface of the retina, which can become contractile and subsequently create a traction detachment.

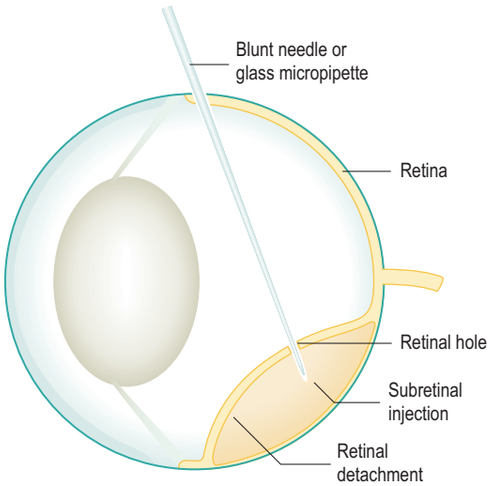

Figure 71.2 Rhegmatogenous detachments can be created in animal models by the injection of fluid between the neural retina and underlying retinal pigmented epithelium. The pipette or needle will leave a hole in the retina that will remain open and even expand, creating the retinal break characteristic of this type of detachment.

1

Box 71.1

Rhegma, derived from Greek, refers to a break in continuity

2

Box 71.2

Central serous retinopathy (CSR) or central serous choreoretinopathy results from serous detachment of the macula. It occurs most commonly in middle-aged males. The mechanisms are poorly understood. These detachments usually, but not always, resolve spontaneously. Even those that do resolve can have lasting effects on vision[1]

3

Box 71.3

A monograph, *Retinal Detachment*, prepared in 1979 for the American Academy of Ophthalmology,[3] is a valuable resource describing much of the history associated with the diagnosis, symptoms, and treatment of detachment. It is referenced here although out of print, because copies exist in libraries and used copies presumably can be found for sale. Much of the historical information presented here is derived from that source

4

Box 71.4

A scleral buckle consists primarily of a band or bands of material, now usually silicone rubber and/or silicone sponges in a variety of configurations surgically placed to encircle the globe and to indent the wall of the eye in the region of the detachment.[6] A scleral buckle is used in conjunction with cyrotherapy or laser treatment to seal the retinal break

5

Box 71.5

The gases sulfur hexafluoride (SF_6) and perfluoropropane (C_3F_8) are commonly used in pneumatic retinopexy

credited with moving an inevitably blinding condition into a treatable one. The next major advance occurred 70 years later when Custodis described the "scleral buckle"[6] (Box 71.4).

This technique achieved a success rate of between 75 and 88%.[7] In the early 1970s Norton[8] described the use of "pneumatic retinopexy," or injection of an expanding gas bubble into the vitreous cavity (Box 71.5) to reappose the retina and RPE (once these tissues are moved into close physical proximity, natural adhesive forces will usually cause them to reattach[9]). There is still much ongoing discussion on the use of scleral buckling, primary vitrectromy, and pneumatic retinopexy[6,7,10–12] to treat rhegmatogenous RD.

The success rate for rhegmatogenous RD after one surgical procedure is now cited as in the range of 80–95%.[7] That number rises closer to 95% if a second reattachment procedure is performed.

Surgical success refers to a reapposition of the sensory retina and RPE and does not refer specifically to the return of vision. Redetachment by traction on the retina and imper-

fect vision can both occur after successful reattachment. The goal of experimental detachment in animal models is gaining an understanding of underlying cellular mechanisms that will presumably aid in developing improvements in the treatment of the primary detachment as well as the means for preventing the occurrence of secondary tractional RD.

Epidemiology

The incidence of rhegmatogenous RD is described as anywhere from 1 in 10 000 to 1 in 15 000 in the general population. This translates to a prevalence of about 0.3% or approximately 1 in 300 patients over the course of the average patient lifetime. The risk levels for RD vary slightly among different studies but there is general agreement that if ocular trauma is factored out, the prevalence among men and women is about equivalent.

Prognosis and complications

Rhegmatogenous RD is still the condition most frequently treated by retinal surgeons (H. Heimann, personal communication). About 5% of reattachments fail for unknown reasons. Traction detachment caused by proliferative vitreoretinopathy (PVR: the growth of cellular "membranes" on the retinal surface) remains the most common reason for failure, with a rate of 7–10% in primary surgeries and even higher when a second procedure is necessary.[2,13,14] Many studies have shown significant effects of rhegmatogenous RD on functional vision after successful repair. Burton[15] and Tani et al[16] estimated that 30–40% of reattachment patients do not achieve reading ability. A variety of studies estimate that 50% require low-vision aids in order to achieve reading ability (H. Heimann, personal communication). While functional recovery after reattachment is remarkable, it is also true that there is room for improvement.

The development of PVR or subretinal fibrosis (growth of cellular membranes in the subretinal space, i.e., on the photoreceptor surface) is probably the most ominous complication of reattachment. The incidence of PVR is well documented, but that of subretinal fibrosis is not because of the difficulty of resolving these fine cellular membranes by ophthalmic exam. The cellular membranes that form are complex, consisting of at least glial cells, macrophages, and RPE cells. Their attachment to the retina (whether on the vitreal or photoreceptor surface) and contraction can cause wrinkling and redetachment (Figure 71.1). Subretinal fibrosis also effectively blocks the regeneration of outer segments in animal models.[17] PVR was named without a clear link to the actual process of cell division. Indeed, this link is suggested by a variety of data, but not proven. Both cell growth (hypertrophy) and actual proliferation probably play a role (see below). The demonstration that detachment stimulates intraretinal proliferation of all nonneuronal cell types,[18,19] coupled with the assumption that proliferation is generally a part of scar formation, makes antiproliferative agents attractive prospects for preventing or controlling these conditions. Clinical trials with the common antiproliferative drug, 5-fluorouracil (5-FU), proved disappointing,[20] but other antiproliferative agents are providing more encouraging results in animal models.[21] Evidence in mice lacking the expression of glial fibrillary acidic protein (GFAP) and vimentin demonstrates that inhibitors of these intermediate filament proteins may lead to better treatment of the proliferative diseases because subretinal scars do not form in these animals.[22] There are currently no such agents available for medical use. The only therapy for PVR or subretinal fibrosis is surgical removal of the cellular membranes, but even successful removal may lead to disappointing results and carries its own risk. PVR is covered at greater length in Chapter 78.

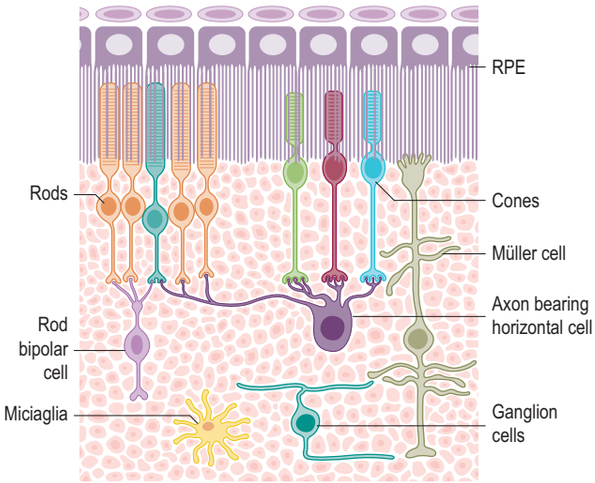

Figure 71.3 Cell types that have been shown to respond to retinal detachment include the retinal pigmented epithelium, rod and cone photoreceptors, rod bipolar cells, axon-bearing horizontal cells, ganglion cells, Müller cells, and microglia.

Pathology

For many years the degeneration of photoreceptor outer segments was recognized as the main cellular pathology of RD. The migration of RPE cells from the monolayer and glial cell expansion to form fibrotic lesions or scars on the retina was also recognized in early pathological studies. More detailed studies by electron microscopy and especially the use of immunohistochemical labeling and confocal imaging have revealed many complex cellular responses to detachment extending through all retinal layers (Figure 71.3).

Reattachment was assumed to return the retina to its "normal" state based on early observations of outer-segment regeneration ("After surgical reattachment the receptor cell outer segments regenerate, the discs assume a normal pattern, and the phagosomes again return to the retinal pigment epithelial cells"[3]). Reattachment instead results in what has been referred to as a "patchwork"[17,23] of recovery across the RPE–photoreceptor interface (Figures 12 and 13 in Fisher et al[24]).

Etiology

Aging, myopia, local retinal atrophy (i.e., lattice degeneration), and cataract surgery are all well-recognized factors that increase risk of detachment. Less common factors

include congenital eye disease, retinoschisis, uveitis, diabetic retinopathy, premature birth, inflammation, or a family history of detachments[25] (http://www.nei.nih.gov/health/retinaldetach/index.asp#5). In some cases there is a clear association with inherited diseases (Norrie disease, Stickler's syndrome, X-linked retinoschisis) while in other cases a role for inheritance may be suggested but poorly understood. The database, Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim), provides information suggesting many potential roles for inheritance in RD. Predicting risk in an individual is complex because of the number of interacting factors that can come into play. Although there have been major improvements in cataract surgery this procedure still produces a significant increase in risk for rhegmatogenous RD.[26] Vitreous liquefaction and posterior vitreous detachment (PVD), which produces traction on the retina, are key pathogenic mechanisms in rhegmatogenous RD.[25,27] Before the age of 60, about 10% of patients experience PVD, while this number rises to about 25% between the ages of 60 and 70 and to slightly over 60% in patients over the age of 80. Epidemiological data suggest that the incidence of detachment begins to rise in the fourth decade of life. There is presently no method for preventing vitreous liquifaction and subsequent PVD. Prophylactic vitrectomy or scleral buckle is rarely performed. Laser photocoagulation or cryotherapy is used around retinal breaks or sites of obvious viteroretinal adhesion to increase chorioretinal adhesion and prevent subsequent detachment but the results are not unequivocal.[27] The prevention of detachment in eyes at risk is a worthy research goal.[27]

Pathophysiology

In recent years it has been recognized that effects of RD occur well beyond the RPE–photoreceptor interface and range from rapid changes in gene expression and protein phosphorylation to neuronal remodeling.[28–32] Many changes described in animal models (Figure 71.4) have been validated in data from human detachment specimens.[33]

The retinal pigmented epithelium

The responses of the RPE monolayer to detachment have not been extensively studied. Its two most prominent responses are proliferation and loss of specialized apical microvilli.[9,34,35] Proliferation begins within a day of RD. A combination of proliferation and migration of the cells can result in complex layers or assemblies in the subretinal space. These do not appear to hinder outer-segment regeneration after reattachment if their orientation is correct.[17] The RPE regenerates de novo its apical microvilli after reattachment, including those highly specialized to ensheath cones. The nature of the signal that induces regeneration is unknown.

Photoreceptors

Until recently, photoreceptors received the most attention in experimental studies of detachment. It is their regenerative capacity that allows the recovery of vision after reattachment. Outer-segment regeneration is a manifestation of the ongoing outer-segment renewal process.[36] In the detached retina the outer segments of both rods and cones degenerate relatively rapidly, within a day, but the two cell types react differently in other ways. For example, rods continue synthesizing proteins specific to their outer segments, while cones appear to shut down this process.[37] Detachment evokes a series of events in photoreceptors that has been described as "deconstruction"[38] (Figure 71.1) to reflect the fact that the whole cell is affected, often resulting in apoptotic death[39] mediated by caspase activation.[40]

The accumulation of opsin in the plasma membrane is a sensitive indicator of outer-segment damage[41] (Figure 71.1). It also provides a good comparison of rods and cones. Rods show the presence of opsin in their plasma membrane in detachments of a month or more in duration. Cones, however, show the presence for a short period of time, usually 3–7 days.[24,37] Photoreceptors lose the distinct compartmentalization of organelles in their inner segments and show a decrease in their mitochondrial population.[39] Many rod synapses are withdrawn into the outer nuclear layer and their ultrastructural organization is distinctly altered, suggesting almost certain changes in the flow of information from rods to second-order neurons[41,42] (Figure 71.5).

After reattachment rod terminals begin repopulating the outer plexiform layer. This regrowth appears to be imperfect after 28 days of reattachment and perhaps accounts for lingering visual deficits in some reattachment patients. Some rod axons regrow beyond their target layer and into the inner retina in both experimental and human RD. This event also occurs in the early development of mammalian retina, suggesting that reattachment reinitiates some developmental programs.

Second- and third-order neurons

The withdrawal of rod synaptic endings raises the question of the response by cells that connect to them: rod bipolar and axon-bearing horizontal cells. There is no evidence for cell death among inner retinal neurons; however confocal imaging shows clearly that these cells remodel the processes that connect them to rod photoreceptors. Rod bipolar cells show rapid neurite sprouting with fine thread-like processes extending deep into the outer nuclear layer, usually terminating near withdrawn rod terminals.[43] Dendrites are probably pruned from these cells as well. Axon-bearing horizontal cells in feline retina rapidly upregulate their expression of neurofilament protein and the axon terminal portion of the cell sprouts neurites that grow into the outer nuclear layer (Figure 71.6). Many of these terminate near withdrawn rod terminals. Others, however, grow along reactive Müller's glia into the subretinal space where they can extend for great lengths along subretinal glial scars.[24]

A subpopulation of ganglion cells, those with the largest cell bodies, undergo dramatic changes that mirror the responses of horizontal cells. They upregulate the expression of two proteins, GAP 43 and neurofilament protein, both of which are expressed at low levels in adult ganglion cell bodies and dendrites[30] (Figure 71.6). The same population sprouts neurites as they structurally remodel. These neurites are extensive and may grow from the cell base into the vitreous, or across the retina and into the subretinal space. In all cases the aberrant processes that grow out of the neural retina are structurally associated with gliotic Müller cell scars.

Thus the detachment of the neural retina from the RPE initiates a series of events in neurons throughout the retina,

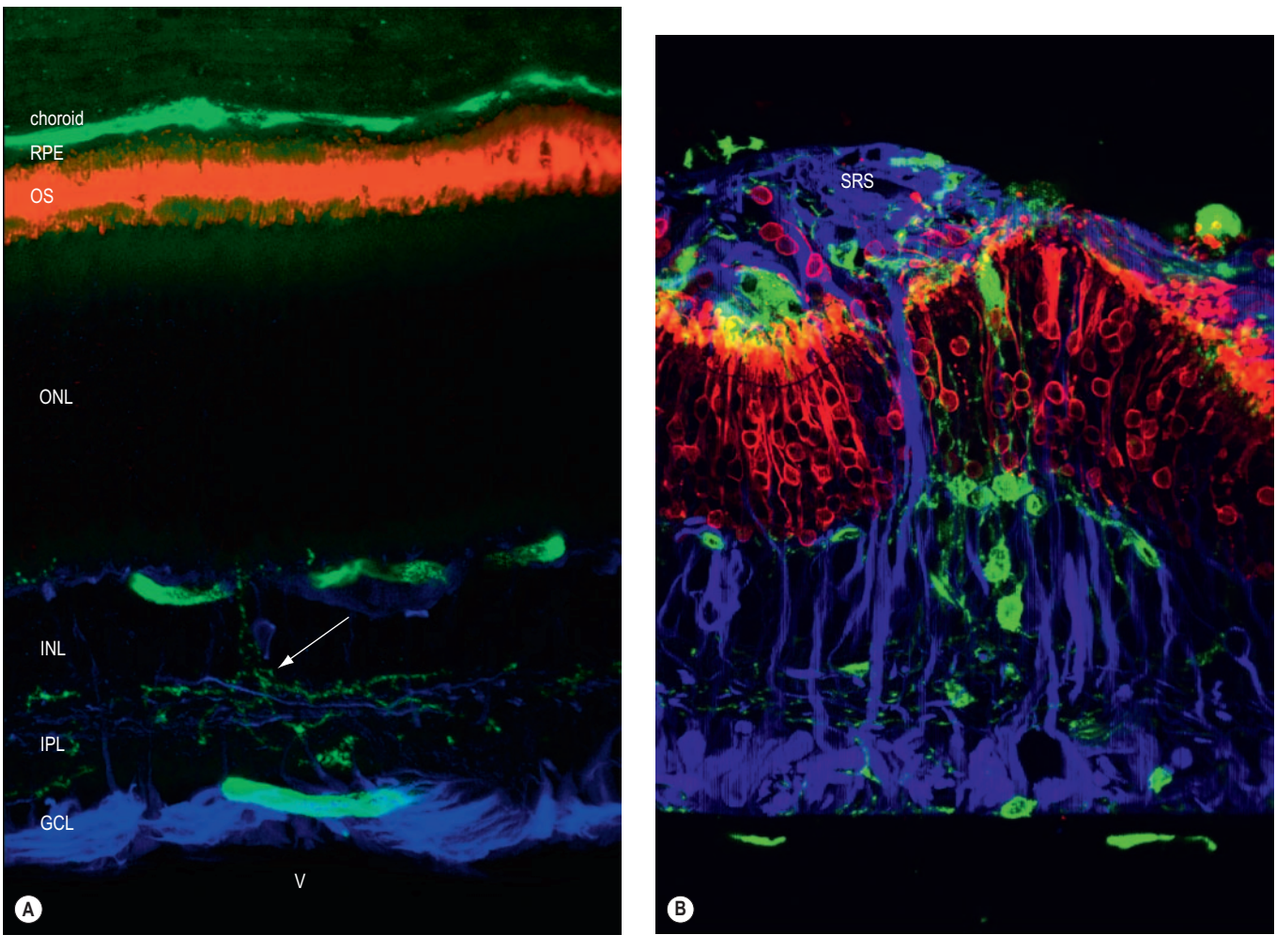

Figure 71.4 Laser scanning confocal microscope images of immunocytochemical labeling demonstrating reactions of the retina to experimental detachment. Sections of normal (A) and detached (B) feline retina labeled with antibodies to rod opsin (red) and glial fibrillary acidic protein (GFAP, blue), and the isolectin, B4 (green). In the normal retina labeling with the rod opsin antibody is limited to the outer-segment (OS) layer which is apposed to the retinal pigmented epithelium (RPE). Anti-GFAP labels only the astrocytes among the optic axon and ganglion cell (GCL) layers. Isolectin B4 labels the stellate microglia (arrow) in the inner retina. In a retina detached for 28 days, rod outer segments have degenerated, and rod opsin is now found distributed in the plasma membrane around the rod cell bodies in the outer nuclear layer (ONL). Müller cells (the radial blue processes) are now heavily labeled with the anti-GFAP. These cells hypertrophy in response to injury and can grow into the subretinal space (SRS) where they form a glial scar. Microglia become reactive and migrate into the outer retina. Macrophages (which also label with the isolectin) enter the SRS. Note that some rod photoreceptors (red) have moved into the SRS in the region of the large glial scar. v, vitreous cavity; IPL, inner plexiform layer; INL, inner nuclear layer. Scale bar = 20 m.

not just among photoreceptors. Ensuing changes in synaptic circuitry could have a profound effect on retinal function and there is evidence that the activity of ganglion cells is abnormal in the detached feline retina (Minglian Pu, personal communication). The reorganization of synaptic circuitry after reattachment may underlie the long-term changes in vision that are known to occur in many reattachment patients.

Müller cells

Müller cells are the complex radial glia of the retina (Figure 71.3). In simplest terms, Müller cells can be thought of as monitoring and regulating the retinal environment, and thus playing a critical role in normal retinal function.[44] They also become highly reactive to detachment, showing changes in early-response genes within hours,[29,31] and changes in structure and protein expression within a day. They proliferate, with a peak response reached 3–4 days after detachment, but continuing at a low level thereafter (Figure 71.7). These cells also undergo a stereotypical structural remodeling that results in the formation of glial scars on both surfaces of the retina, thus contributing to (and perhaps initiating) the diseases subretinal fibrosis and PVR (see Fisher et al[24] for a review).

Müller cells alter their expression pattern for many proteins, including the enzymes glutamine synthetase and carbonic anhydrase, the retinoid-binding protein CRALBP, and the cytoskeletal proteins tubulin, GFAP, and vimentin. An accumulation of the latter two is a hallmark response of these cells to retinal injury (Figures 71.4, 71.6, and 71.7). While intermediate filaments are often regarded as scaffold proteins, there is increasing evidence that they do more. Mice lacking the expression of both ($vim^{-/-}GFAP^{-/-}$) show less photoreceptor cell death after detachment.[45] The same knockout strain does not form subretinal scars after detach-

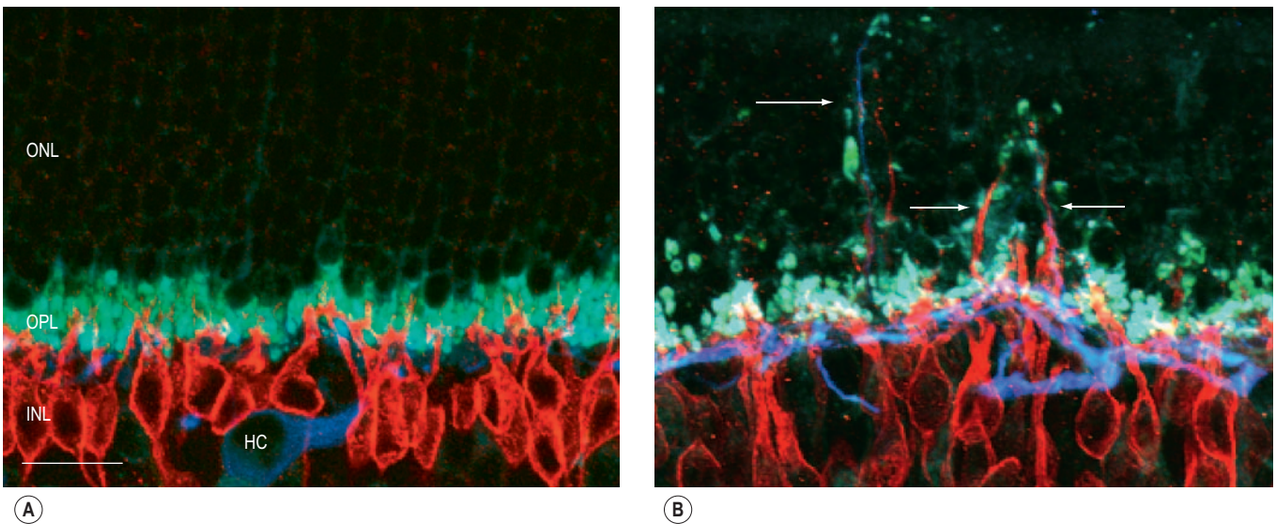

Figure 71.5 Laser scanning confocal microscope images demonstrating additional reactions to experimental detachment. Normal (A) and detached (B) feline retina. Photoreceptor synaptic terminals labeled with an antibody to synaptobrevin (green) form a distinct layer on the border of the outer plexiform layer (OPL). Rod bipolar cells, labeled with an antibody to protein kinase C (red) have their dendrites extending into the synaptic invaginations of the rod synaptic terminals. Axon-bearing horizontal cells (HC), labeled with an antibody to calbindin (blue), are also postsynaptic to rods. After detachment there is a rapid retraction of many rod axons so that their terminals now lie in the outer nuclear layer (ONL), disrupting the layering of the OPL. As rod terminals withdraw, fine neurites grow from both rod bipolar (arrows) and horizontal cells (double arrow) into the ONL (other examples shown in Figure 71.6), demonstrating the remodeling of rods and second-order neurons in response to detachment. INL, inner nuclear layer. Scale bar = 20 m.

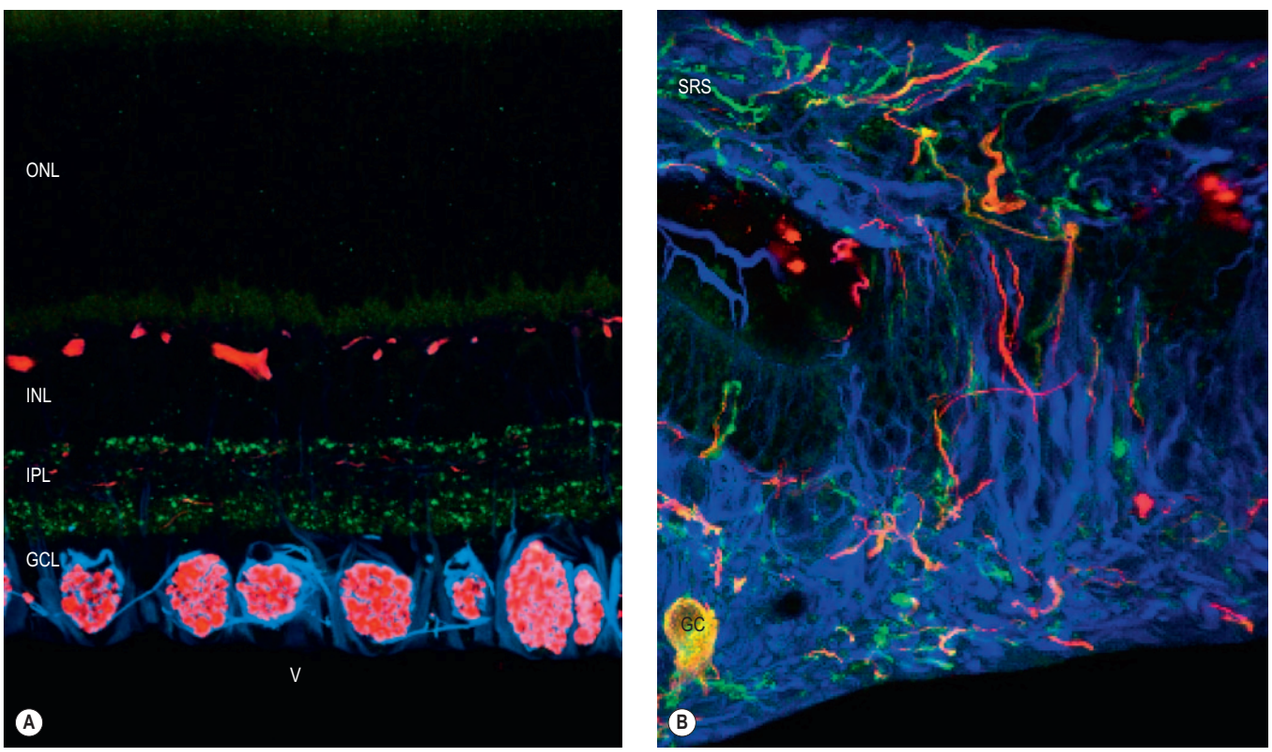

Figure 71.6 Reactions of various cell types to experimental detachment. In a normal feline retina (a) antineurofilament antibody (red) labels ganglion cell axons between the ganglion cell layer (GCL) and vitreous cavity (v), a subset of horizontal cell processes on the border of the inner nuclear layer (INL) and a few fine ganglion cell dendrites in the inner plexiform layer (IPL). An antibody to GAP43 labels sparsely arrayed dendrites of ganglion cells in the IPL. Anti-glial fibrillary acidic protein (GFAP, blue) heavily labels the astrocytes among the ganglion cell axons. After 1 month of detachment, Müller cells have upregulated GFAP expression and in some areas undergone hypertrophy and grown into the subretinal space (SRS) to form glial scars. Many GAP43-positive processes are found throughout the retina and in the subretinal scar. These neurites arise from ganglion cell bodies that re-express GAP43 in response to detachment. These cells, like the horizontal cells, also begin to express neurofilament protein heavily. The yellow ganglion cell (GC) is labeled with antibodies to both GAP43 and neurofilament protein. Neurites from both ganglion cells and horizontal cells course through the area of increased GFAP expression and into the glial scar in the SRS. IPL, inner plexiform layer; ONL, outer nuclear layer. Scale bar = 20 m.

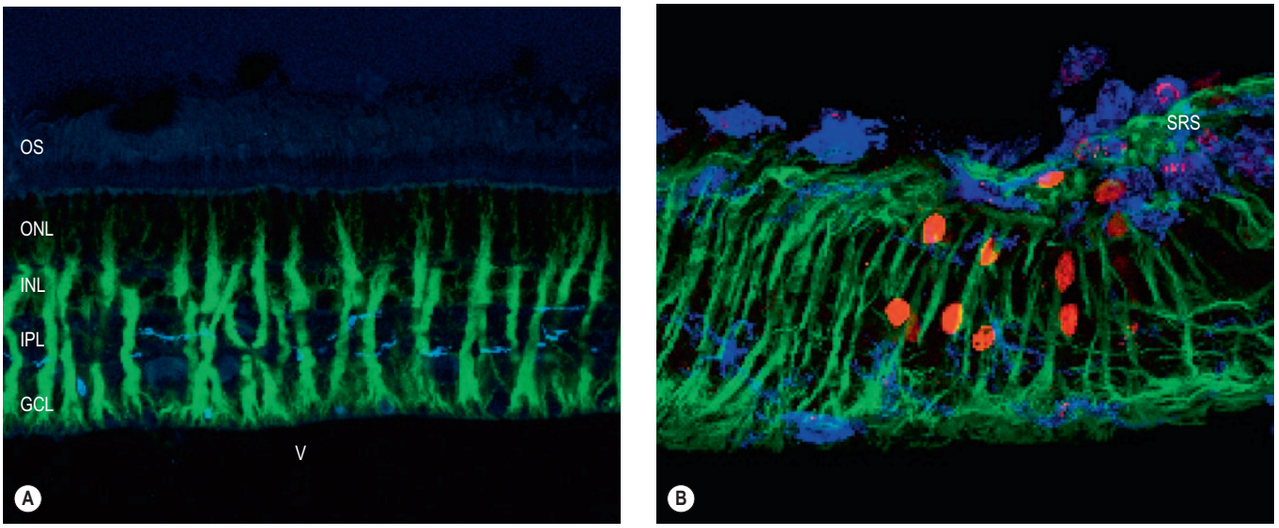

Figure 71.7 Laser scanning confocal microscope images demonstrating the proliferative response to detachment. Normal (A) and 7-day detached (B) rabbit retina are labeled with antibodies to vimentin (green), and bromodeoxyuridine (BrdU, red) as well as with the isolectin B4 (blue). BrdU labels the nuclei of cells undergoing division. In normal retina (A), BrdU-labeled cells are almost never encountered, vimentin extends throughout the cytoplasm of Müller cells, and microglia (blue) are limited to the inner retina. In the detached retina, BrdU labels the nuclei of many cells with some remaining in the inner nuclear layer (INL) while others have migrated into the outer nuclear layer (ONL) and into the large glial scar formed by hypertrophic Müller cell processes (green) in the subretinal space (SRS). A relationship between Müller cell proliferation and glial scar formation is suggested by data of this type. Reactive microglia migrate throughout the retina while macrophages, which also label with the isolectin, enter the SRS. v, vitreous cavity; GCL, ganglion cell layer; IPL, inner plexiform layer. Scale bar = 20 m.

ment.[22] An association between the upregulation of these proteins and expansion of the Müller cells seems obvious when observing the changes by immunocytochemistry (Figures 71.4, 71.6, and 71.7). There are also data suggesting that the predominant intermediate filament protein expressed in a Müller cell will determine whether they grow into the vitreous cavity or subretinal space.[25]

Proliferation, intermediate filaments, subretinal fibrosis, and PVR

Both PVR and subretinal fibrosis are considered "proliferative diseases," and yet the link between the diseases and the actual proliferation of any cell type is weak. Bromodeoxyuridine (BrdU) labeling studies show that nuclei of Müller cells synthesizing DNA on the third day after detachment have migrated into subretinal membranes by day 7 (Figure 71.7). It seems logical that this correlation could be extrapolated to Müller cells forming membranes on the vitreal surface, but there are no actual experimental data. Thus, as mentioned earlier, agents that prevent proliferation or those that reduce intermediate filament synthesis may reduce the risk for these complications or even cause their regression, thus reducing the need for secondary surgical procedures.

Microglia and the immune response

Microglial cells are immune cells that in their unactivated state reside in the inner retina. After detachment they proliferate, assume a rounded shape, and migrate into the photoreceptor layer where they scavenge dead or dying cells.[46] Microglia may cause or prevent photoreceptor cell death by modulating the release of trophic factors from Müller cells.[47] Macrophages from the circulation enter the subretinal space, where they also scavenge debris from degenerated outer segments (Figures 71.4, 71.6, and 71.7). Microarray analysis of mRNA expression in porcine retinas detached for 24 hours identified significant increases in the expression of many genes involved in the immune and inflammatory responses.[32] In reattached retina the presence of microglia correlates strongly with the degree of photoreceptor recovery.[42] The immune system's role in detachment is only beginning to be appreciated.

In summary, rhegmatogenous RD remains a serious retinal problem that can result in long-lasting visual deficits. The study of animal models and comparisons to data from human tissue are providing new information at the cellular and molecular levels that may help understand why successful anatomical reattachment can still leave a patient with imperfect vision,[48] or why some detachments lead to PVR while others do not.

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