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PATHOGENESIS OF NEOVASCULARIZATION IN THE RETINA AND CHOROID

Ophthalmology, K. Mizuno, editor

Interrelationships of the choriocapillaris, retinal pigment epithelium, and retina

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The fundus of the eye is composed of three separate anatomic entities, namely: the neurosensory retina, the retinal pigment epithelium (RPE), and the choroid. While these are distinct and separable tissues, they function together and must be considered as allied components of the visual system.

Because it is the receptor of the photon, and thus the first link in vision, the neurosensory retina is the pre-eminent ocular tissue. However, it cannot exist in splendid isolation; it requires nutrition, a constant milieu, a waste elimination system, and biologic anchoring to the back of the eye. The eye is harmoniously constructed to allow light from the outside world to be accurately focused and then properly processed so that the electrical impulses which reach the visual centers of the brain can reconstruct our surroundings. So precisely aligned are the retinal outer elements of both eyes that a single complex image is formed within our head. An image filled with color, detail, and dimensionality.

In this article I will give a personal overview of the interrelationships between the retina and its neighbors and also some thoughts about the retina itself.

The triad

There is an intimate anatomic and functional relationship between the choriocapillaris (CC), Bruch's membrane, and the RPE. This triad has been termed the *tunica ruyschiana*, after the famous Dutch anatomist, Ruysch, who lived during the late 17th and early 18th century. In a sense, Bruch's membrane anchors the RPE into a strict position with regard to the percipient elements and also fixes the CC so that the overlying RPE receives a continuous and adequate supply of blood. The CC acts to take away heat generated by light striking the outer retina photopigments and, more importantly, that absorbed by the RPE. Without this heat sink, the outer retina would burn up. Furthermore, the RPE may be the most active cellular monolayer in the body and therefore requires an unimpeded supply of oxygen and other nutrients.

The choriocapillaris

Until relatively recently, the generally accepted concept was that the choroidal capillaries formed a continuous network without any anatomic or functional

divisions. Experimental observations by my colleagues and me (1) suggested that this was not the case, and that at least functionally there were numerous interlaced vascular lobules. Later anatomic and experimental observations (2, 3) supported this point of view, and today most ophthalmologists believe that there is a segmental choroidal capillary network in man and animals. While still a matter of argument I feel that the weight of evidence upholds this view. The pattern of discrete lobular filling of the CC is most evident upon high-speed fundus fluorescein angiography, especially if the intraocular pressure is elevated. The fundus appearance in certain disorders such as acute multifocal posterior placoid epitheliopathy, choroidal involvement in systemic hypertension, some examples of giant cell arteritis, and many types of choroiditis, further strengthens the argument for a segmental nature of the CC.

Each CC lobule at the posterior pole appears to be about 250 micra or more in diameter – that is about 1/5 to 1/4 of a disc in diameter – with a central feeding terminal arteriole and a series of peripheral draining veins. I estimate that a single choroidal vascular unit may be responsible for nourishing several hundreds of RPE cells. Block the choroidal arteriole responsible for one CC lobule and you em barrass all the overlying RPE cells.

The CC possess some interesting anatomic properties: they are of very wide caliber compared to other capillaries, they exist as a rather strict monolayer, and they have fenestrae with an odd orientation. The fenestrae normally face Bruch's membrane and the RPE rather than the choroidal stroma and sclera. This suggests that their nutritional output is directed to the RPE and overlying photoreceptors. The fact that, in cases of choroidal malignant melanoma, the fenestrae may orient themselves towards the neoplasm (4) is suggestive of the labile nature of CC fenestrae. Furthermore, recent work from our department demonstrates that the RPE appears to be able to modulate the form and function of the CC (5–7). For example, without the RPE the CC first lose their fenestrae, then they close down and eventually atrophy. These observations led us to speculate that in human situations where the CC is absent this may well occur secondary to RPE degeneration and not vice versa.

Bruch's membrane

Bruch's membrane acts mainly as an architectural scaffolding uniting the CC and RPE. Anatomically it is a pentalaminar structure whose inner and outer portions are the basement membranes of the RPE and CC, respectively. Bruch's membrane thickens with age mainly because of the incremental nature of basement membranes in general (in the eye similar examples of thickening with age are the lens capsule, Descemet's membrane, and vascular basement membranes). While Bruch's membrane may seem to be rather dense and impenetrable on light- and electron-microscopic evaluation, such is not the case. It only prevents the largest substances that traverse the CC fenestrae from reaching the RPE. Certainly with aging, the nature of the membrane changes and its central elastic core and the surrounding collagen undergo calcific degeneration. The role of such changes in fundus pathology is not clear. It is our distinct impression that Bruch's membrane is no barrier to vascular invasion from the choroid. Given sufficient stimulation, choroidal vessels readily penetrate the membrane and grow into the sub-RPE space.

Since Bruch's membrane is mainly a supportive unit for the immediately surrounding tissues, it is not surprising that trauma sufficient to rupture it will create a tear both in the overlying RPE and the underlying CC. Most so-called 'choroidal' tears are in reality mainly breaks in Bruch's membrane.

Retinal pigment epithelium

Regarded with little clinical or scientific interest until relatively recently, the RPE is one of the most important and fascinating tissues of the body. Initially conceived of as little more than an inert monolayer of pigmented cells with little function other than to intercept light making its way past photoreceptors, it is presently recognized that the RPE does the following:

1. It is the anatomic anchor for rods and cones, its processes surrounding the outer segments and presumably aiding in their orientation. Should the RPE become detached, the overlying retinal elements are displaced and the eye experiences a distortion transmitted to the brain. Following repair of a retinal detachment, the RPE once again grasps the outer segments.

2. It is a remarkable 'garbage' dump. Until the mid-1960s, mainly through the work of Young (8), it was totally unknown that outer segments of the photoreceptors were capable of shedding and replacement. The RPE is responsible for cleaning up the immense amount of retinal debris which is apparently shed in a diurnal rhythm. Perhaps it is the RPE that determines the cycle of shedding and its volume. For example, in subretinal fluid following rhegmatogenous detachments, I am unaware that one finds shed outer segments. The RPE-outer segment attachment under normal conditions is anatomic-phagocytic if you will.

3. The RPE absorbs light. Photons that pass beyond the visual pigment trap are captured by the RPE so that stray light does not bounce back to initiate an unfocused or scattered image.

4. It stores and processes vitamin A, the key biochemical substance for vision.

5. It modulates the function of the CC. This important facet, just recently appreciated, is discussed above.

6. The RPE acts as the outer blood-retinal barrier. Until the mid- to late-1960s there was no appreciation of the fact that the RPE was really equivalent to the tight junctioned endothelium of retinal blood vessels. Now it is well appreciated, mainly as a result of the widespread use of fluorescein angiography, that the RPE is an important barrier to substances that leave the CC and cross Bruch's membrane. The tight junctions girdling the RPE cells and holding them strongly together form the main exclusionary zone. Break down the RPE barrier and the outer retina is subjected to a disordered internal milieu.

7. The RPE undoubtedly has the ability to pump fluid from the subretinal space into the choroid. It must do this in an active manner to maintain RPE-neural retina approximation.

8. The RPE is capable of migrating into the retina, liberating macrophagic cells, and causing scar formation.

It is quite interesting to examine what the RPE does *not* do. It apparently does not produce pigment much if at all after fetal life; it does not seem to regenerate by mitotic activity; it seems to heal defects mainly by sliding across bare areas; and it does not produce metastasizing neoplasms (neither does the lens epithelium nor the corneal endothelium!).

There are somewhere between 4 to 6 million RPE cells lining the posterior portion of the optic cup. Each RPE cell is responsible for anchoring, nurturing, and biologically grooming some 30 to 45 photoreceptors (or perhaps more in the foveal region). Destroy a single RPE cell and you hinder numerous rods and cones.

Thus, to this point I hope it is clear that the tissues composing the *tunica ruyschiana* interrelate and are essential for proper neuroretinal functioning.

The retina

With regard to the retina itself, there is an interesting but often overlooked point. There are said to be approximately 130 million photoreceptors – perhaps 6 million being cones, but only about 1 million consisting of ganglion cells and their nerve fibers which exit the eye. Thus, there is more than a 2 log unit difference between the neural elements in the outer and inner retina. This suggests that there must be marked integration within the middle portion of the retina, an area worthy of further exploration. In this age of computers the retina itself turns out to be a first-rate and very sophisticated one: it allows tens of millions of impulses to be integrated in a fashion that a million or less electrical signals can enter our brain and display for us the glory that we call vision.

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Ophthalmology, K. Mizuno, editor

Choroidal neovascularization: it takes more than a break in Bruch's membrane*

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Until recently, ophthalmic clinicians, pathologists, and researchers paid very little attention to the subject of choroidal neovascularization. Now, however, the situation has changed dramatically and choroidal vessels are implicated in a wide number of ocular fundus disorders. This article reviews the subject of choroidal neovascularization as it is presently conceived, and points out the areas in which information is either scant or lacking.

What is choroidal neovascularization?

We define choroidal neovascularization, often called subretinal neovascularization (SRN), as the growth of blood vessels from the already mature choroidal vascular bed into adjacent areas not normally associated with such vessels. The exact origin of the new blood vessels from the choroidal vascular bed is not known; they presumably emanate from choroidal capillaries or the small terminal venules. Thus, choroid-derived blood vessels found within Bruch's membrane, between Bruch's membrane and the retinal pigment epithelium (RPE), between the RPE and the neural retina, or in the outer neural retina, are considered to be examples of choroidal neovascularization. Retinochoroidal or chorioretinal vascular anastomoses are not included in this definition, nor are fibrovascular choroidal scars secondary to perforating injuries. It is presently unknown whether intrachoroidal neovascularization, analogous to intraretinal microvascular abnormalities, occurs.

What is the significance of choroidal neovascularization?

We believe that many cases of choroidal neovascularization may be 'silent' and have little or no clinical significance, however, if such vessels rupture or leak abnormally they may cause damage to the adjacent RPE and/or neural retina leading to either transient or permanent visual impairment. In certain conditions, usually involving the macula (macular degeneration associated with aging and often miscalled 'senile' macular degeneration, presumed ocular histoplasmosis syndrome [POHS], angioid streaks, and so-called 'choroidal' rupture) a newly formed choroidal vascular network (it is unusual, clinically, to see more than a single network) penetrates Bruch's membrane, comes to lie between this membrane and the RPE, proliferates,

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and has a tendency to bleed. On the other hand, there appear to be many examples of choroidal new vessels which seem to be relatively quiescent, and rarely hemorrhage. Examples of the latter are seen histopathologically at the retinal periphery, in the juxtapapillary area, and within some drusen of the fundus.

How common is choroidal neovascularization?

Both the prevalence and incidence of human choroidal neovascularization are unknown. It is most often noted in autopsy eyes of elderly individuals (at least in Caucasians), it is probably present in all instances of disciform macular degeneration, and may occur with varying frequency in relationship to a large number of posterior pole fundus disorders (Table 1). In our opinion, choroidal neovascularization is the most common example of intraocular neovascularization, being far more frequent than retinal, optic nerve head, or iris neovascularization (1).

Where are choroidal 'new' vessels found?

(The quotation marks around *new* alert us to the fact that such vessels may either have appeared recently or be of long duration.) Presumably, these vessels may emanate at any point of the choroid. Our present knowledge suggests that asymptomatic choroidal neovascularization, i.e. without bleeding or abnormal leaking, is most frequently found (histopathologically) at the far retinal periphery (2); it is less frequently noted in the peripapillary region, and is least frequent at the macula. On the other hand, symptomatic choroidal new vessels, i.e. those that leak either blood or blood-borne products beneath the RPE or retina, are most common in the macular region, less frequent around the disc, and least often noted at the far periphery. It is presently unknown whether the structural make-up or function of the new choroidal vessels is similar at the different loci where they occur.

Why has choroidal neovascularization received little attention until recently?

Duke-Elder reviewed the subject of choroidal neovascularization up to 1966 (3). Evidently, choroidal neovascularization eluded the attention of clinicians up to that point in time. Even histopathological material on the subject was scant and for the most part, the presence of such new choroidal vessels was considered secondary to prior hemorrhaging (similarly, at that time many ophthalmologists felt that retinal neovascularization occurred secondary to hemorrhage rather than vice versa). Gass was the first to suggest that choroidal neovascularization might be seen on fluorescein angiography (4). He did not imply at that time that such vessels were a common pathogenetic feature of disciform macular degeneration or other disorders. However, his observations lay the groundwork for further studies. The epochal papers of Teeters and Bird (5, 6) demonstrated the frequent finding of choroidal neovascularization in macular degeneration; they further indicated that such vessels could often be detected by clinicians using direct ophthalmoscopy or slit-lamp fundus examination. From that point on, numerous other conditions, mainly involving the macular region, have been noted to have choroidal neovascular nets as an associated feature (Table 1). The exact relationship of the new vessels to these disorders is not clear, but the visible presence of such vessels often suggests to clinicians an ominous prognosis. In her excellent studies, Sarks has confirmed the common presence of neovascularization arising from the choroid in elderly individuals (7, 8).

TABLE 1
Conditions associated with choroidal neovascularization.

Macula
Acute multifocal placoid pigment epitheliopathy
Aging change*
Angioid streaks*
Behçet's disease
Best's vitelliform degeneration
Butterfly dystrophy of the RPE
Central serous chorioretinopathy
Choroidal folds
'Choroidal' (Bruch's membrane) rupture*
Choroidal tumors
Hemangioma
Malignant melanoma
Metastases
Nevi
Osteoma
Choroiditis
Coccidioidomycosis
Disciform macular degeneration*
Fundus flavimaculatus
Harada's disease
Myopic degeneration – Förster-Fuchs' spot*
Photocoagulation
Argon laser
Experimental photic injury
Xenon
POHS*
Postscleral buckling and drainage
Puerperal sepsis
RPE detachment*
Rubella
Sarcoidosis
Serpiginous choroiditis
Sickle cell disease
Toxocariasis
Toxoplasmosis
Optic disc
Drusen*
Optic pits
Papilledema
Periphery
Aging change*

Adopted from: Charles, Gartner and Henkind. Choroidal neovascularization. In preparation.
*Common relationship.

What is the pathogenesis of choroidal new vessel formation?

The pathogenetic mechanism or cause(s) of new vessel formation from the choroid, either in aging or ocular disease processes, is presently unknown. Several points are clear. First, choroidal neovascularization generally occurs by itself, that is without

other evidence of ocular neovascularization. For example, choroidal neovascularization, regardless how extensive, is not accompanied by nor does it provoke overlying retinal neovascularization, and it does not seem to relate to iris neovascularization (1). Conversely, retinal neovascularization, regardless of extent, does not seem to stimulate choroidal neovascularization. Secondly, ocular hypoxia, often invoked as a major causative agent of retinal, optic nerve head and iris neovascularization, has not been demonstrated to be a major factor in inducing new vessels from the choroid.

Breaks or dehiscences in Bruch's membrane are thought to be sufficient to cause new vessel formation from the underlying choroid. While this is possible, it is unlikely, for we have seen numerous examples in our pathology laboratory of eyes which contained choroidal breaks (which probably were present during life) and in which new vessels emanating from the underlying intact choroidal circulation were absent. Such breaks are usually extensive and linear (Gartner and Henkind, unpublished data). In cases of SRN associated with aging, the stoma or passage in Bruch's membrane is small and barely wider than the ingrowing vessel. Further, there are numerous clinical cases of traumatic 'choroidal' rupture and many examples of angioid streaks in which there is no clinical evidence of choroidal neovascularization. On the other hand, clinically evident breaks in Bruch's membrane in the macular region seem to be prone to develop new vessels. The macular region is apparently a more susceptible or stimulating site for choroidal new vessel formation, but we do not know why. Thus, it must take more than simply a break in Bruch's membrane to cause choroidal neovasculogenesis.

Chronic inflammatory cells have been postulated to induce choroidal neovascularization in conditions such as POHS, and in macular degeneration associated with aging. While this may have some validity in certain cases, it remains to be proved. Furthermore, most instances of choroidal inflammation in which an array of chronic inflammatory cells can be found are unassociated with choroidal neovascularization. For example, sympathetic ophthalmia, in which various inflammatory cells are abundant throughout the uveal tract, has no associated choroidal neovascularization. Nor does syphilitic chorioretinitis, where one finds retinal elements penetrating Bruch's membrane and coming to lie within the choroid (9).

We believe that the RPE is the tissue responsible for calling forth newly formed choroidal vessels, however, we cannot rule out factors from the macular region of the neural retina. There is now abundant experimental evidence that the RPE can modulate the appearance and presumably the function of vessels adjacent to it (10, 11). Furthermore, the absence of RPE in human and experimental circumstances leads to the disappearance of underlying choriocapillaries (12–14).

At the present time, it would be safe to say that choroidal neovascularization occurs separately from other forms of ocular neovascularization, and that the stimulus is likely a biochemical rather than a mechanical break in Bruch's membrane.

Some clinical examples of choroidal neovascularization

Disciform macular degeneration

Macular degeneration associated with aging is, in our experience, the most common disease in which choroidal new vessels are to be found. Indeed, the new vessel net (which generally appears to be a single network emanating from one point in the central macula) is the essential element which must be present prior to the appearance

of subretinal hemorrhage and its consequent organization which causes a deep fibrovascular-neuroglial scar. We have examined more than 1000 cases of macular degeneration. Most occur in elderly Caucasians; we have seen few cases in blacks, even though our department treats many elderly black individuals. Virtually no cases were seen in Oriental individuals, but this might have been due to the fact that our department only has a small number of Oriental patients. For the most part, the patients suffer from the usual complaints of the elderly with no predilection for any specific systemic disease. Though we treat numerous diabetic patients, we have only found a disciform macular degeneration in a handful of such individuals, and we believe that there is no relationship between the macular degeneration and the diabetes. Most of our patients have bilateral macular degeneration with asymmetry of presentation. We have not seen an individual with a fully developed disciform response in an aging eye who did not have ophthalmoscopic evidence of macular disease (i.e. macular drusen, irregularity of the RPE, or clinical evidence of a neovascular net beneath the RPE) in the contralateral eye. We have never seen a clinical break in Bruch's membrane to precede the neovascular ingrowth, nor have we seen clinical evidence of inflammation in the fundus in such patients. Cataract extraction may exacerbate the condition by turning a rather quiescent macula with evidence of early macular degeneration into a fully formed disciform response.

It is interesting that in our analysis of macular degeneration in the elderly two quite distinct patterns are found: (1) the disciform response which we feel occurs secondary to the neovascular choroidal network bleeding, fibrovascular growth, and blood organizing within the outer retina and RPE, and (2) an atrophic macular change in which the RPE appears to degenerate and melt away, leaving an atrophic macular zone. A patient may be afflicted in one eye with one type of macular change and in the other eye with a different type. We believe that this is evidence to support our hypothesis that it is mainly the RPE which initiates the vascular response from the choroid. The disciform type of response is noted when the RPE is present and often hypertrophic in appearance, while the atrophic macular response occurs where the RPE is either sparse or absent. The latter is often seen in patients with high myopia. Myopia may provide further evidence for the idea that the RPE is essential for calling forth and sustaining new vessels from the choroid. The Förster-Fuchs' spot which mainly occurs in younger individuals, appears to be an attenuated version of a disciform macular degeneration. It occurs in highly myopic patients in the central macula region where the RPE is present, but it rarely is extensive, possibly because the adjacent RPE is sparse. Choroidal new vessels are not seen to develop in areas where the RPE is completely absent.

Optic disc drusen and subretinal/sub-RPE hemorrhage

We have now accumulated about 15 cases of optic disc drusen which have had associated bleeding from newly formed vascular networks derived from the choroidal circulation adjacent to the optic disc margin. The majority have been in young individuals in the first 3 decades of life, the youngest being less than 5 years of age. In most instances, the subretinal and/or sub-RPE bleeding occurred bilaterally and often within a few weeks or months of the first eye being affected (15). Most cases were familial in the sense that disc drusen could be detected in family members. However, only 1 case was found where a mother and her daughter had evidence of hemorrhage with subsequent disciform response. Remarkably, the macular region was the affected area in all but 1 case. We do not know why some of our patients