Müller Cell Cone, an Overlooked Part of the Anatomy of the Fovea Centralis

Hypotheses Concerning Its Role in the Pathogenesis of Macular Hole and Foveomacular Retinoschisis

J. Donald M. Gass, MD

Poorly recognized by anatomists and pathologists is the cone-shaped zone of Müller cells that composes the central and inner part of the fovea centralis. The importance of these cells in the structural integrity of the macula, as a repository for xanthophyll, and in the pathogenesis of macular diseases, particularly regarding idiopathic macular hole and foveomacular schisis, is hypothesized.

ULTRASTRUCTURE OF THE FOVEA CENTRALIS

In 1969, Yamada reported the light and electron microscopic anatomy of the fovea centralis in the eye of a 45-year-old woman. The inner half of the foveola was composed of an inverted cone-shaped zone of Müller cells (Müller cell cone). The truncated apex of the cone was located at the outer limiting membrane, where there were no receptor nuclei (arrowhead, Figure). The base of the cone formed the floor of the fovea centralis and extended into the area of the clivus in the perifoveolar region (arrows, Figure). In the light microscopic thin sections prepared for electron microscopy, the cytoplasm of the Müller cells composing the outer portion of the Müller cell cone appeared optically empty. The cytoplasm became slightly more dense toward the base of the Müller cell cone. The low density of the Müller cell cytoplasm within the cone was evident in electron micrographs and was in contrast to the greater density of Müller cell cytoplasm elsewhere in the retina where the Müller cells were intimately intertwined with the receptor neurites. The Müller cell cone was free of neurites except near its apex, where the long outer cone fibers extended from the outer limiting membrane anteriorly and outwardly in a radiating fashion through Müller cell cytoplasm into the surrounding cone nuclei (arrowhead, Figure). A few nuclei of either atypical glial cells or ectopic ganglion cells were present within the Müller cell cone. Not stated in Yamada’s report was the location of the nuclei of the Müller cells composing the cone. The internal limiting membrane lining the

©1999 American Medical Association. All rights reserved.
inner surface of the Müller cell cone was thin (10 nm to 20 nm) compared with that in the peripheral foveal area (1.5 μm). Hogan and coworkers1 subsequently confirmed Yamada’s findings.

HYPOTHESES

Hypothesis 1: Müller cell cone is a reservoir for retinal xanthophyll. Xanthophyll is concentrated within the cells that make up the Müller cell cone and is partly responsible for the peculiar low density of the cell cytoplasm in this area.

Investigators have found that identifying the exact location of the retinal xanthophyll is difficult. Snodderly and coworkers1 reported that the retinal xanthophyll is most concentrated within the inner part of the foveola and perifoveolar area in what was thought to be the fiber layers (receptor axon layer and inner plexiform layer). Since there is minimal nerve fiber layer in the foveolar area, it is probable that most of the xanthophyll there is present within the Müller cells and accounts for the low density of their cytoplasm within the area of the cone. Likewise, most of the superficial layer of perifoveolar xanthophyll may reside within the cells that compose the base of the Müller cell cone rather than in the inner plexiform layer. The superficial retinal xanthophyll, which extends only a short distance beyond the foveal capillary-free zone into the region of the clivus, is probably responsible for the superficial retinal burns that occur as applications of argon blue-green photocoagulation are placed near the edge of the capillary-free zone. Beyond the perifoveolar region, xanthophyll is largely confined to the outer nuclear and plexiform layers throughout the macula. Xanthophyll becomes progressively less concentrated toward the peripheral macula. The presence of highly concentrated xanthophyll in pseudo-opercula in patients with various stages of age-related macular holes is additional evidence in support of the presence of concentrated xanthophyll in the Müller cell cone.6-7

Hypothesis 2: The Müller cell cone is the primary structural support for the fovea. The Müller cell cone serves as a plug to bind together the receptor cells in the foveola. Without this plug of glial cells, the retinal receptor cell layer with its thin layer of horizontally radiating nerve fibers would be highly susceptible to disruption at the umbo and hole formation under a variety of circumstances, including sensory retinal detachment, minor trauma, cystoid macular edema, and macular degeneration.

Hypothesis 3: The Müller cell cone is a primary role player in age-related macular hole formation. The earliest changes occurring in the development of age-related macular hole involve degeneration of the Müller cell cone–vitreous cortex interface, Müller cell invasion and proliferation within the prefoveolar vitreous cortex, contraction of the prefoveolar vitreous cortex, disruption of the Müller cell cone, full-thickness retinal dehiscence at the umbo, centrifugal retraction of the receptor cell layer, and formation of a prehole opacity.

There is considerable evidence that idiopathic age-related macular hole formation begins with contraction of the prefoveolar vitreous cortex that is tightly adherent to the internal limiting membrane of the Müller cell cone. It is probable that Müller cell invasion and proliferation within the prefoveolar vitreous cortex are important in causing contraction of the prefoveolar vitreous cortex and the sequence of events postulated above. Recently, investigators using optical coherence tomography and scanning electron microscopy to study patients with impending macular holes have demonstrated evidence of a split in the foveola with cyst formation in some patients.8,9 The Müller cell cone provides an anatomical substrate for schisis to occur. A split occurring within the retinal receptor cell layer would be unlikely. Madreperla et al8 and Ezra et al9 studied 20 opercula excised during surgery for stage 3 macular holes. They found native vitreous cortex, as well as Müller cells and/or fibrous astrocytes, in 100% of cases. In approximately 50% they found bits of the inner retina including internal limiting membrane, neuroretina, and some perikarya. This is evidence suggesting that contraction of the prefoveolar vitreous cortex in some cases causes avulsion of the internal limiting membrane, the Müller cell cone, superficial inner cone fibers (Henle layer), and occasionally a few cone nuclei. Failure to find inner retinal elements in 50% of cases suggests that contraction of the prefoveolar vitreous cortex in the absence of avulsion of the inner retina is capable of causing dissolution of the Müller cell cone and dehiscence of the foveola at the umbo. Failure to find large numbers of cone nuclei, outer limiting membrane elements, and inner cone receptors is evidence that horseshoe-shaped foveolar tears and formation of full-thickness retinal opercula occur rarely in age-related macular hole formation. Separation of the vitreous cortex in the perifoveolar area is evident by ultrasound and optical coherence tomography in the normal fellow eyes of some patients with macular holes and in many patients with impending macular holes.8,11 Some authors have suggested that tangential traction exerted on the fovea by the normal...
movement of the vitreous body may be responsible for macular hole development. It is not known, however, whether perifoveal separation of the vitreous is the cause of, the result of, or unrelated to contraction of the prefoveolar cortex.

Hypothesis 4: Congenital abnormalities affecting the Müller cell cone are responsible for the pathognomonic biomicroscopic picture of foveomacular schisis. X-linked juvenile retinoschisis is characterized clinically by peculiar macular changes (foveomacular schisis) in 100% of children and young adults and in approximately 50% of patients by peripheral retinoschisis and so-called vitreous veils. Later in life the delicate superficial radiating network of fine polycystic changes, characteristic of foveomacular schisis, may be replaced by nonspecific atrophic changes. Histopathologically, the splitting of the peripheral retina occurs superficially between the ganglion cell layer and the nerve fiber layer. There is histopathological and ultrastructural evidence that degeneration of the inner portion of Müller cells may be the cause of X-linked juvenile retinoschisis. Unfortunately, none of the eyes examined pathologically had typical foveomacular schisis at the time of enucleation. Before Yamada’s ultrastructural study of the normal fovea, if one considered that there were no Müller cells or ganglion cells and only a few nerve fibers in the foveola, there was no plausible explanation for foveomacular schisis.

Further investigation of the ultrastructure of the fovea centralis in patients of different ages and sex are needed to give us more insight concerning the pathogenesis of age-related macular hole and other disorders affecting the macula.

Accepted for publication November 6, 1998.

This study was supported in part by a Senior Scientific Award from Research to Prevent Blindness Inc, New York, NY.

Reprints: J. Donald M. Gass, MD, Department of Ophthalmology, Vanderbilt University, Medical Center East, Nashville, TN 37232-8808 (e-mail: Donald.Gass@mcmail.vanderbilt.edu).

REFERENCES

From the Archives of the ARCHIVES

A look at the past . . .

MARLOW’s case was an unmarried woman of thirty years who suffered from irregular menstruation. Has had sick headaches all her life, much severer since she was fourteen years old. She had also other attacks, epileptic in character, becoming rigid with some convulsive movements and loss of consciousness for hours. After a correction of her refraction by R + 1.00, + 0.25 D, L + 0.25 D, + 0.75 100°, the attacks ceased. This was five years ago, and there has been no recurrence.