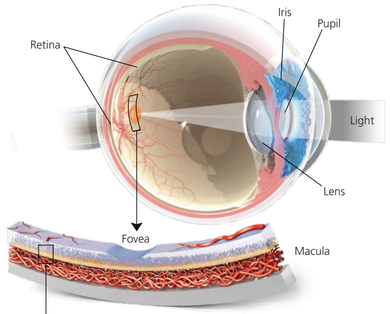
Geographic Atrophy (GA): A Guide for Clinicians

Geographic Atrophy (GA) is the advanced atrophic form of Age-related Macular Degeneration (AMD). GA is a leading cause of visual impairment among elderly people, affecting 5 million people worldwide, including 22% of people over 90 years old. While there are no approved treatments currently available, recent advances in our understanding of AMD mechanisms and risk factors provide a host of potential targets for drug development.



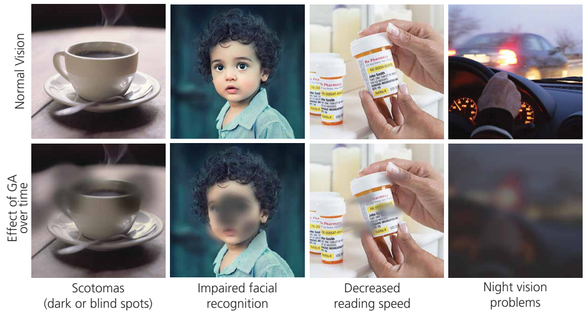
Risk Factors

Risk factors for GA include:
- Advanced age (especially over 85)
- Early AMD to GA present in fellow eye
- Smoking
- Genetic polymorphisms

Genetic Risk Factors:
Most of the genetic risk for AMD and GA is linked to polymorphisms in complement genes CFH, CFI, C2/CFB, C3, and C9. The other major gene involved in GA is ARMS2.

Symptoms

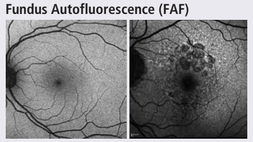
GA progression causes a gradual loss of visual function in patients. Symptoms include the presence of scotomas (large dark or blind spots in the visual field), difficulty recognizing faces, decreased reading speed (measured in words per minute), impaired dark adaptation, impaired contrast sensitivity, and difficulty driving at night.



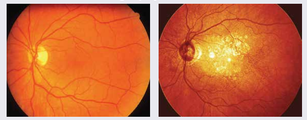
Clinical Diagnosis

Several imaging methods are used, often in combination, to assess and diagnose geographic atrophy cases. Atrophic lesions are characterized by confluent areas of retinal pigment epithelium (RPE) and photoreceptor cell death, often with a sharp demarcation from healthy retinal tissue. Studies have used varying size definitions to classify GA, with minimum affected area measurements ranging from 10μm to 250μm. GA most commonly starts around the center of the macula. As the lesion expands into the fovea, visual function severely decreases.

Fundus Autofluorescence (FAF)

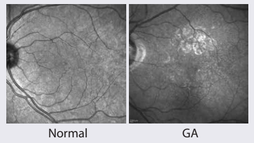


Color Fundus Photography (CFP)

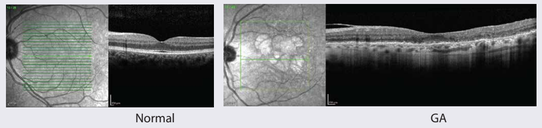


GA lesions include areas of increased visibility of choroidal vessels.

Near Infrared Reflectance Imaging (NIR)



Optical Coherence Tomography (OCT)



The OCT scan corresponds with the horizontal green line on the accompanying image.

Progression of AMD to Geographic Atrophy

Retinal Maintenance in Healthy Eyes

In the healthy retina, the retinal pigment epithelium (RPE) and choriocapillaris support the activity of the photoreceptors. The RPE cells manage waste buildup, oxygen and nutrient transport, and cytokine secretion.

Age-Related Changes in the Retina

The high metabolic demands of the photoreceptors combined with their photo-oxidation waste products result in oxidative stress in the retinal microenvironment. Lipoproteinous deposits called drusen accumulate under the RPE.

Pathogenesis of AMD

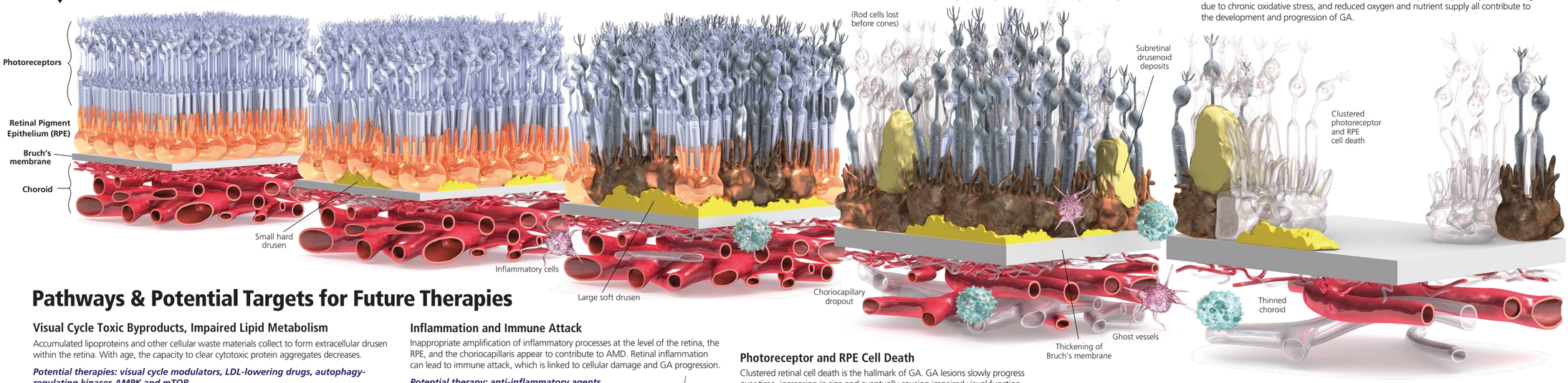
It is thought that excessive accumulation of lipofuscin results in the appearance of large, soft drusen, marking the early pathogenesis of AMD. Increased inflammatory proteins may lead to activation of the alternative complement pathway.

Progression of AMD

The local inflammatory microenvironment and dysregulation of the alternative complement pathway may lead to cell death and increased inflammation. Subretinal drusenoid deposits (SDD) form between the RPE and photoreceptor cells, Bruch's membrane thickens, and photoreceptor, RPE and choriocapillaris dropout occurs.

Geographic Atrophy

AMD has progressed to GA when well-defined patches of loss of the RPE, photoreceptors and choriocapillaris are observed. Atrophic lesions expand over time and become visible via diagnostic imaging. It is hypothesized that a combination of inflammation in the retinal microenvironment, immune attack via the alternative complement pathway, DNA damage due to chronic oxidative stress, and reduced oxygen and nutrient supply all contribute to the development and progression of GA.

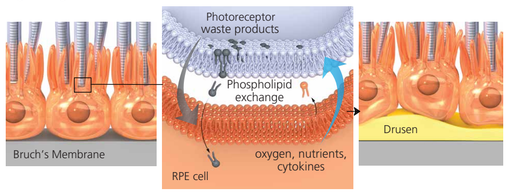


Pathways & Potential Targets for Future Therapies

Visual Cycle Toxic Byproducts, Impaired Lipid Metabolism

Accumulated lipoproteins and other cellular waste materials collect to form extracellular drusen within the retina. With age, the capacity to clear cytotoxic protein aggregates decreases.

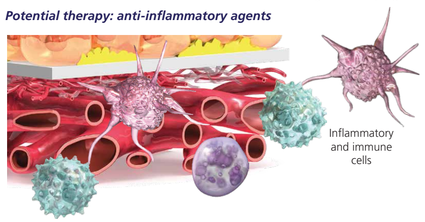
Potential therapies: visual cycle modulators, LDL-lowering drugs, autophagy-regulating kinases AMPK and mTOR



Inflammation and Immune Attack

Inappropriate amplification of inflammatory processes at the level of the retina, the RPE, and the choriocapillaris appear to contribute to AMD. Retinal inflammation can lead to immune attack, which is linked to cellular damage and GA progression.

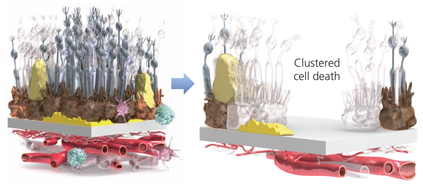
Potential therapy: anti-inflammatory agents



Photoreceptor and RPE Cell Death

Clustered retinal cell death is the hallmark of GA. GA lesions slowly progress over time, increasing in size and eventually causing impaired visual function.

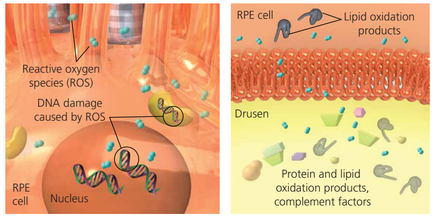
Potential therapy: cell replacement therapy



Chronic Oxidative Stress

The retina is exposed to high levels of sunlight and oxygen, which causes oxidative stress in the inner retinal environment. Oxidative stress can directly lead to DNA damage in affected cells, and can indirectly lead to inflammation and immune attack.

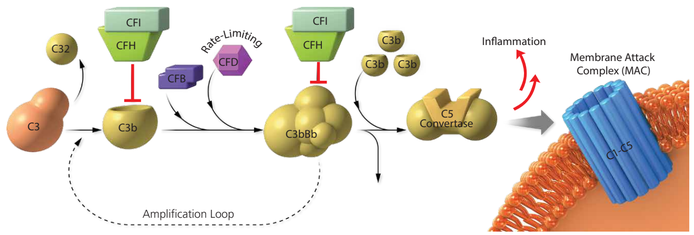
Potential therapies: antioxidants, neuroprotectants



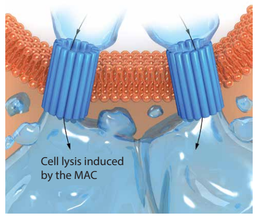
Alternative Complement Pathway Dysregulation

A low level of complement activation is necessary for immune surveillance in the eye. Dysregulation of the alternative complement pathways leads to self-complement attack, resulting in increased inflammation that can contribute to AMD progression.

Potential therapy: alternative complement pathway inhibitors



The RPE and choriocapillaris can be targeted for destruction via formation of the Membrane Attack Complex (MAC).



Clinical Trials

Phase II and III clinical trials for GA therapies are ongoing, employing strategies such as complement factor D (CFD) inhibition, cell replacement therapy, neuroprotection, and delivery of neurotrophic factors.

For more information, visit www.cinicaltrials.gov.

Endpoints for GA Clinical Trials

GA can progress slowly and lesions can enlarge significantly before reaching the fovea. Changes in alternative measures of visual function may be identified in patients before deterioration occurs in best-corrected visual acuity (BCVA), such as maximum reading speed (words per minute, wpm), and low luminance visual acuity (LLVA). Patient-reported outcome (PRO) measures that demonstrate good internal consistency and reliability should also be considered for use in GA clinical trials, such as the Functional Reading Independence (FRI) Index and the NEI VFQ-25.

The most comprehensive, reliable, and objective measures for tracking disease progression in patients with GA are anatomic endpoints using imaging methods such as color fundus photography (CFP), fundus autofluorescence (FAF), near infrared reflectance (NIR), and optical coherence tomography (OCT). Clinical studies should assess both anatomic progression and visual function.

The Angiogenesis Foundation

Center of Excellence for Retinal Disorders
geographicatrophy.org

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