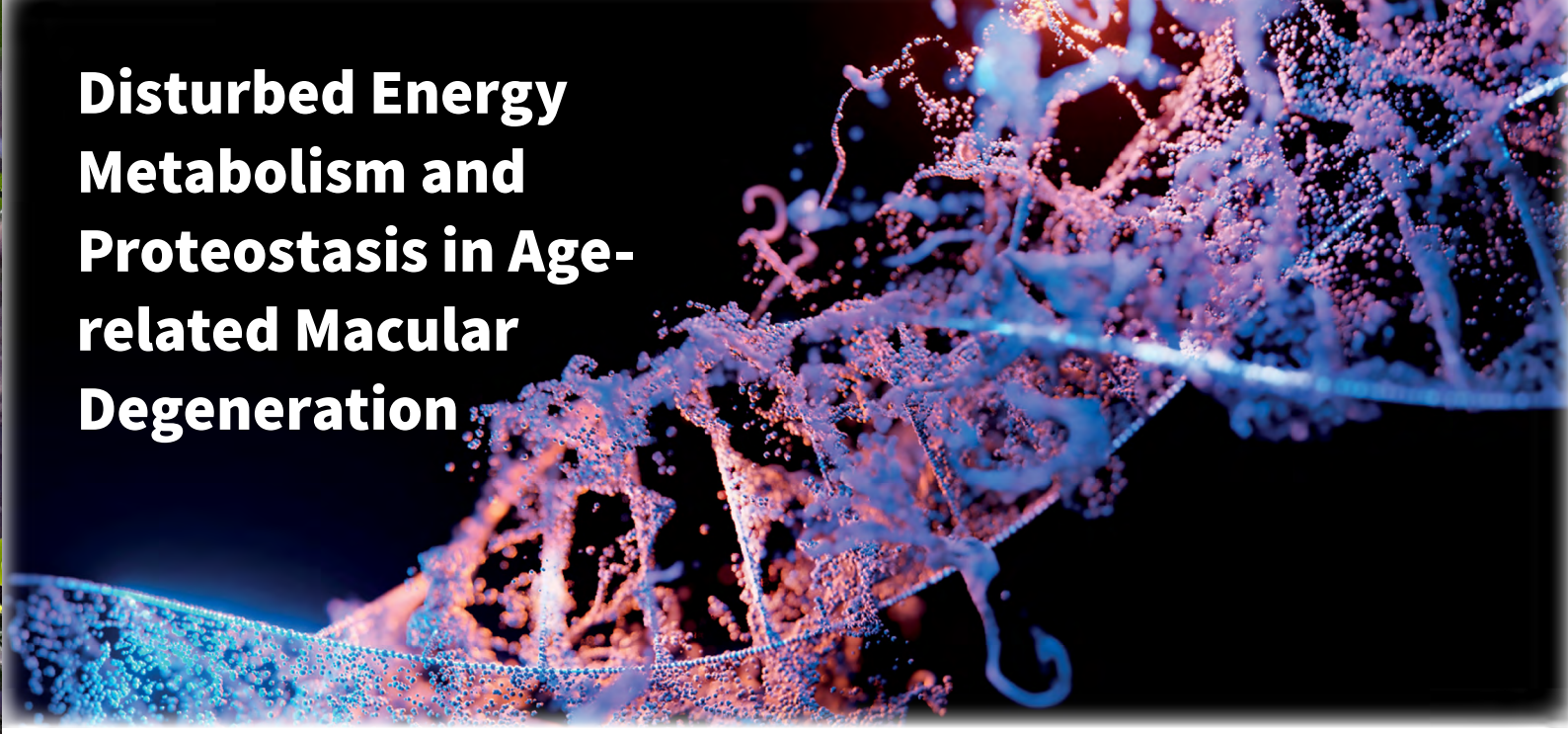
# Disturbed Energy Metabolism and Proteostasis in Age-related Macular Degeneration



The etiology of age-related macular degeneration (AMD) is known to be multifactorial. Genes associated with AMD involve pathways that regulate energy metabolism, protein aggregation, inflammation, and neovascularization. Better understanding of the cross-talk among genetic risk factors, environmental risk factors, molecular mechanisms, and clinical phenotype in AMD may provide new tools for improved diagnosis, treatments, and risk-based prevention strategies.

The accumulation of protein deposits, such as intracellular lipofuscin and extracellular drusen, in AMD is an indication of disturbed protein homoeostasis.[1] Protein homeostasis, known as "proteostasis," includes the integrated pathways of protein synthesis, folding, translocation, and degradation. The Nobel Committee's decisions in Physiology or Medicine during the past decades indicate the importance of the proteolytic mechanism. Christian de Duve (Belgium; 1917–2013), Albert Claude (Belgium; 1898–1983), and George Palade (Romania; 1912–2008) won a Nobel Prize for uncovering the structural and functional organization of the cell in 1974. Aaron Ciechanover (Israel), Avram Herscko (Hungary), and Irwin Allan Rose (USA;

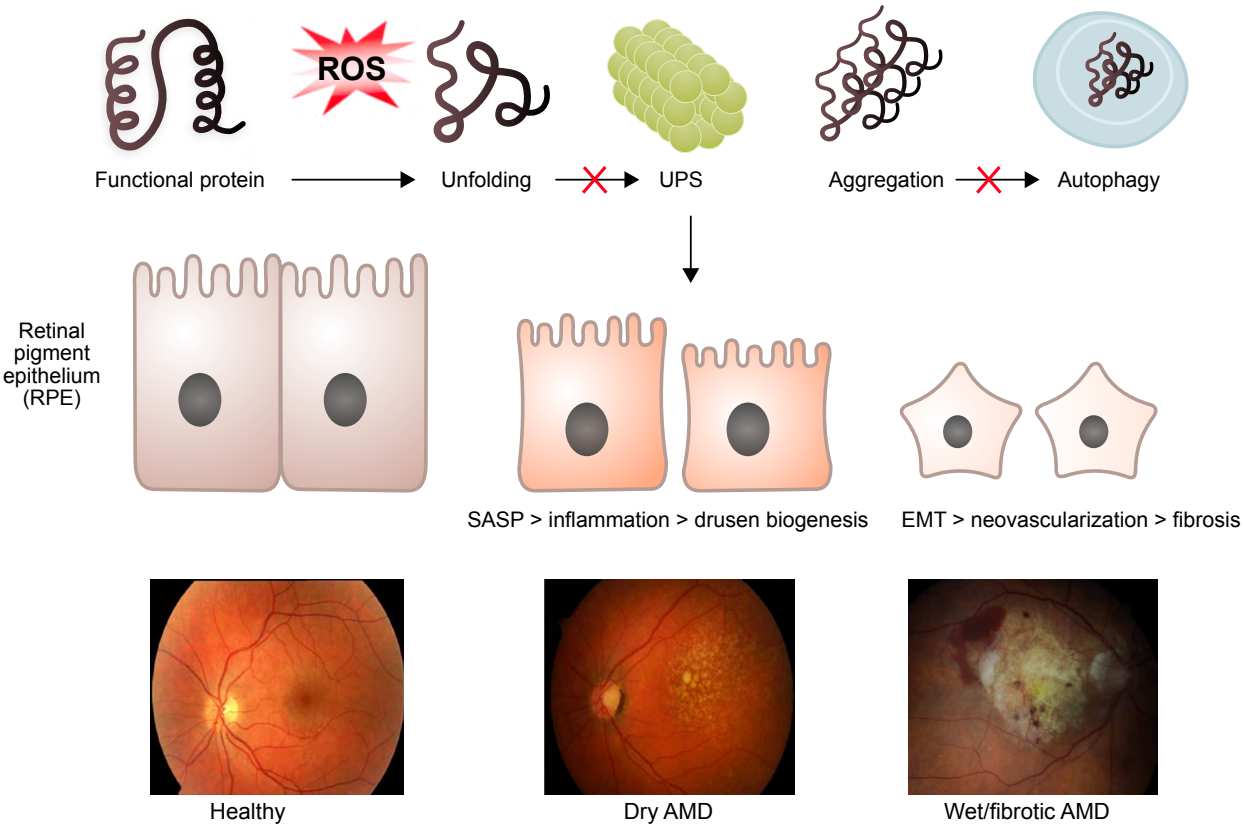



*Figure 1. Progression of AMD results in the increased production of ROS and protein misfolding together with disturbed proteasomal and autophagy clearance. RPE phenotype changes lead to advanced AMD signs.* ***Abbreviations****: AMD, age-related macular degeneration; UPS, ubiquitin-protesomal system; EMT, epithelial–mesenchymal transition; SASP, senescence-associated secretory phenotype; ROS, reactive oxygen species; RPE, retinal pigment epithelium.*

1926–2015) earned their Nobel Prize in 2004 for elucidating the ubiquitin–proteasome system (UPS). Professor Yoshinori Ohsumi (Japan) recently won the 2016 Nobel Prize for his efforts in lysosomal autophagy research.

The macula is exposed to a high metabolic rate, high oxygen pressure, and continuous reactive oxygen species (ROS) production.[2] At present, chronic oxidative stress, mitochondrial dysfunction, and impaired autophagy are strongly linked to the pathogenesis of AMD,[3] and oxidative stress-induced damage to the retinal pigment epithelium (RPE) is considered a key factor in AMD pathology. The UPS and lysosomal autophagy pathways are the two major proteolytic systems that remove damaged proteins and organelles, and these proteolytic pathways are supported by the transcription factors nuclear factor erythroid 2-related factor-2 (NFE2L2) and peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α), which control the regulation of antioxidant enzymes and biogenesis of mitochondria. We have developed models of AMD in which RPE degeneration leads to AMD-related pathological changes when autophagy and NFE2L2/PGC-1α are suppressed.[4] Decreased autophagy or NFE2L2/PGC-1α responses are associated with cellular senescence.[4-5] In AMD, the accumulation of lipofuscin in the RPE is a sign of senescence, and the senescence-associated secretory phenotype (SASP) coincides with the release of ROS, selective growth factors, and inflammatory cytokines, chemokines, and proteases.[3] In addition, the RPE may switch on the epithelial–mesenchymal transition (EMT) because of malfunctioning of various pathways and processes that are required to maintain homeostasis. The EMT is a process in which polarized epithelial cells change their structural and biochemical properties to become more motile and adaptable mesenchymal cells. These EMT-related changes have been observed in AMD.[5-6] Disturbed intracellular proteostasis, together with the SASP and EMT, may accelerate secretory autophagy—a recently recognized pathway that is involved in drusen biogenesis and chronic inflammation during AMD progression.[3]

In conclusion, genetic and environmental risk factor studies do not sufficiently explain the differences in progression between dry and wet AMD phenotypes, as well as differences in treatment responses between patients. Thus, there is a need to understand the mechanisms that lead to different cellular phenotypes and their functions in the choriocapillaris and retina.

***Key points:***

- Mitochondrial dysfunction leads to disturbed proteostasis in AMD.
- Autophagy plays a key role in AMD pathology.
- Impaired autophagy is linked to chronic inflammation, SASP, and EMT in AMD.
- Secretory autophagy may open new ways to understand drusen biogenesis and AMD progression.

# Oslo Society of Ophthalmology Honorary Lecture Series

*This article is a summary of the Oslo Society of Ophthalmology Honorary Lecture 2022 delivered by Professor Kaarniranta. The Oslo Society of Ophthalmology, established in 1915, invites outstanding scientists to deliver lectures. Selected presentations are published in Oftalmolog.*

***Kai Kaarniranta***
***Department of Ophthalmology, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland; Department of Molecular Genetics, University of Lodz, Lodz, Poland***

***References***

1. Kaarniranta K, et al. Mechanisms of mitochondrial dysfunction and their impact on age-related macular degeneration. Prog Retin Eye Res. 2020 Nov;79:100858.
2. Stefánsson E, et al. Metabolic physiology in age related macular degeneration. Prog Retin Eye Res. 2011 Jan;30(1):72-80
3. Kaarniranta K, et al. Autophagy in age-related macular degeneration. Autophagy. 2023 Feb;19(2):388-400.
4. Felszeghy S, et al. Loss of NRF-2 and PGC-1α genes leads to retinal pigment epithelium damage resembling dry age-related macular degeneration. Redox Biol. 2019 Jan;20:1-12.
5. Blasiak J, et al. Epithelial-Mesenchymal Transition and Senescence in the Retinal Pigment Epithelium of NFE2L2/PGC-1α Double Knock-Out Mice. Int J Mol Sci. 2021 Feb 8;22(4):1684.
6. Liukkonen MPK, et al. Epithelial-mesenchymal transition-related serum markers ET-1, IL-8 and TGF-β2 are elevated in a Finnish wet age-related macular degeneration cohort. Acta Ophthalmol. 2022 Aug;100(5):e1153-e1162.