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MD Research News

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Drug treatment

Retina. 2014 Mar 26. [Epub ahead of print]

MULTILAYERED PIGMENT EPITHELIAL DETACHMENT IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Rahimy E, Freund KB, Larsen M, Spaide RF, Costa RA, Hoang Q, Christakopoulos C, Munch IC, Sarraf D.

PURPOSE: To describe the spectral domain optical coherence tomography findings in eyes with chronic fibrovascular pigment epithelial detachment (PED) receiving intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy.

METHODS: Retrospective observational case series of patients with chronic fibrovascular PEDs receiving serial intravitreal anti-VEGF therapy. Corresponding spectral domain optical coherence tomography scans of chronic PEDs were studied in detail over multiple visits. The internal structure within the sub-PED compartment was analyzed, characteristic features were identified, and then correlated with visual outcome.

RESULTS: Thirty-eight eyes of 34 patients with fibrovascular PEDs were included. Mean and median Snellen visual acuity was 20/50 (range, 20/20-20/400). Eyes received a mean of 28.2 intravitreal anti-VEGF injections (median, 23.0; range, 3-70) administered over a mean of 36.9 months (median, 37.5; range, 6-84). A fusiform, or spindle-shaped, complex of highly organized layered hyperreflective bands was noted within each PED. Nineteen eyes demonstrated heterogenous, dilated, irregular neovascular tissue adherent to the undersurface of the retinal pigment epithelium. Additionally, 25 eyes demonstrated a hyporeflective cavity separating the choroidal neovascularization complex from the underlying choroid.

CONCLUSION: Chronic fibrovascular PEDs receiving serial anti-VEGF therapy demonstrate a characteristic fusiform complex of highly organized, layered, hyperreflective bands, termed a "multilayered PED," which is often seen in conjunction with neovascular tissue adherent to the undersurface of the retinal pigment epithelium monolayer. On the basis of previous histopathologic correlations, these bands may represent a fibrous tissue complex with contractile properties. An associated hyporeflective space, termed a "pre-choroidal cleft," separates the fusiform complex from the underlying choroid and may be due to contraction, the exudation of fluid, or both. Many of these eyes maintain good visual acuity, presumably because the neovascular and cicatricial process is suppressed within the sub-retinal pigment epithelium space by chronic anti-VEGF therapy, thus permitting the viability of the photoreceptor population through preservation of the retinal pigment epithelium.

PMID: 24675391 [PubMed - as supplied by publisher]

J Fr Ophtalmol. 2014 Mar 20. pii: S0181-5512(14)00065-5. doi: 10.1016/j.jfo.2013.08.006. [Epub ahead of print]

Intravitreal ranibizumab for neovascular age-related macular degeneration patients with good baseline visual acuity and the predictive factors for visual outcomes.

Ozkaya A, Alkin Z, Osmanbasoglu OA, Ozkaya HM, Demirok A.

PURPOSE: To evaluate the efficacy of intravitreal ranibizumab for the treatment of neovascular age-related macular degeneration (nAMD) patients with a visual acuity (VA) of ≥20/40 and to investigate the predictive factors for visual outcomes.

METHODS: The present study is a retrospective analysis of patients with VA≥20/40. Injections were given monthly for the first 3 months and thereafter as needed. The patients were divided into two groups; group 1, patients not receiving further injections beyond the 3 loading doses, and group 2, those who received further injections. Next, group 2 was divided into two subgroups; group 2A, patients who did not experience VA loss, and group 2B, those who experienced VA loss. Data collected for each patient included VA and central retinal thickness (CRT) measured at baseline, months 3, 6, 9, and 12.

RESULTS: The study included 96 eyes of 96 patients. Change in VA showed a significant inverse correlation with total number of injections at month 12 (r=-0.34, P=0.001), and the presence of pigment epithelial detachment (PED) at baseline (r=-0.35, P<0.01). VA outcomes were better in group 1 than group 2 at all time points (P<0.001 for all). Change in VA at month 3 was not significantly different between groups 2A and 2B (P=0.26); however, change in VA at month 6, 9, and 12 were statistically different between the two groups (P<0.001 for all).

CONCLUSION: Intravitreal ranibizumab is an effective treatment for nAMD patients with good VA. The presence of PED, need for reinjection, and VA loss were unfavorable prognostic factors.

PMID: 24657215 [PubMed - as supplied by publisher]

J Med Econ. 2014 Mar 28. [Epub ahead of print]

A United Kingdom-based Economic Evaluation of Ranibizumab for Patients with Retinal Vein Occlusion (RVO).

Taylor M, Serbetci E, Ferreira A, Gairy K, Lewis L, Blouin J, Mitchell P.

Abstract Objective: This study compares the cost-effectiveness of intravitreal ranibizumab versus observation and/or laser photocoagulation for treatment of macular oedema secondary to retinal vein occlusion in a UK-based model.

Methods: A Markov model was constructed using transition probabilities and frequency of adverse events derived using data from the BRAVO, CRUISE and HORIZON trials. Outcomes associated with treatments and health states were combined to predict overall health costs and outcomes for cohorts treated with each option.

Results: In branch retinal vein occlusion, ranibizumab produced a gain of 0.518 quality-adjusted life years at an incremental cost of £8141, compared with laser photocoagulation. The incremental cost-effectiveness ratio was £15 710 per quality-adjusted life year, and the incremental cost per month free from blindness was £658. In central retinal vein occlusion, ranibizumab produced a gain of 0.539 quality-adjusted life years at an incremental cost of £9216, compared with observation only. The incremental cost-effectiveness ratio was £17 103, and the incremental cost per month free from blindness was £423.

Conclusions: These incremental cost-effectiveness ratios are below the £20 000-30 000 range typically accepted as a threshold for cost-effectiveness. This suggests that ranibizumab may be regarded as a cost-effective therapy for patients with macular oedema secondary to retinal vein occlusion, relative to grid laser photocoagulation (for BRVO) and observation (for CRVO). Limitations include sparse data for utilities

associated with the severity of visual impairment in the WSE in patients with RVO. A lack of direct comparative evidence between ranibizumab and the dexamethasone intravitreal implant for the treatment of BRVO and CRVO and the infeasibility of an indirect comparison due to significant heterogeneity in trial designs prevented the inclusion of this treatment as a comparator in the Markov model.

PMID: 24673384 [PubMed - as supplied by publisher]

Retina. 2014 Apr;34(4):629-35. doi: 10.1097/IAE.0000000000000116.

SYSTEMIC SAFETY OF RANIBIZUMAB FOR DIABETIC MACULAR EDEMA: Meta-analysis of Randomized Trials.

Yanagida Y, Ueta T.

PURPOSE: To evaluate systemic safety of ranibizumab for diabetic macular edema.

METHODS: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov were systematically reviewed. Eligible studies were randomized trials on ranibizumab for diabetic macular edema with observation at least 6 months and ≥80% completion rate that reported systemic adverse events of cerebrovascular accident, myocardial infarction, vascular death, and overall mortality. The numbers of adverse events were compared between patients treated with ranibizumab and those without. Furthermore, dose-dependent effect of ranibizumab was estimated for overall mortality through Poisson meta-regression.

RESULTS: Six trials with 2,459 patients were included. All trials had exclusion criteria on systemic vascular conditions for enrollment. Risk ratio for cerebrovascular accident, myocardial infarction, vascular death, and overall mortality were 0.80 (95% confidence interval, 0.37-1.73; P = 0.57), 0.91 (95% confidence interval, 0.46-1.80; P = 0.78), 1.29 (95% confidence interval, 0.58-2.86; P = 0.53), and 1.92 (95% confidence interval, 0.78-4.73; P = 0.16), respectively. Poisson regression model showed a significant dose-dependent increase in overall mortality in the largest randomized trial using monthly ranibizumab (P = 0.04). However, the significance disappeared (P = 0.133) when pooled with other studies using ranibizumab on pro re nata basis.

CONCLUSION: Ranibizumab for diabetic macular edema is considered safe when the patients are carefully selected based on systemic vascular conditions and it is used on pro re nata basis. Further evaluation is necessary on more intensive use or on high-risk patients.

PMID: 24667549 [PubMed - in process]

Curr Opin Ophthalmol. 2014 Mar 21. [Epub ahead of print]

Long-term longitudinal study of patients treated with ranibizumab for neovascular age-related macular degeneration.

Rasmussen A, Sander B.

PURPOSE OF REVIEW: To review the current literature regarding long-term treatment beyond 2 years with anti-vascular endothelial growth factor (VEGF) inhibition for neovascular age-related macular degeneration (nv-AMD).

RECENT FINDINGS: Only few studies of anti-VEGF treatment for nv-AMD exist beyond 2 years, and the number of patients followed for 4 years or longer is small. The results of studies show that the majority of patients with nv-AMD can preserve visual acuity compared with baseline, subgroups reveal large variations in visual benefit. Approximately 20-30% of patients seem to respond poorly to the treatment, and 20% obtain a condition with inactivity and good results. The majority of patients will need continuous active treatment. Long-term decline of visual acuity reflects the natural progression of the disease, however, insufficient treatment cannot be excluded leaving a potential for further improvement. Close follow-up to detect recurrent activity of nv-AMD and activity in fellow eye is important. Definitive evidence of systemic

side-effects is lacking, but long-term VEGF inhibition seems to be tolerated well with few ocular and systemic complications.

SUMMARY: The majority of patients with nv-AMD can preserve visual acuity and expect long-term treatment beyond 2 years. Ocular complications and systemic adverse events remain few.

PMID: 24663065 [PubMed - as supplied by publisher]

Ophthalmologica. 2014 Mar 19. [Epub ahead of print]

Microaneurysm Turnover in Diabetic Retinopathy Assessed by Automated RetmarkerDR Image Analysis - Potential Role as Biomarker of Response to Ranibizumab Treatment.

Leicht SF, Kernt M, Neubauer A, Wolf A, Oliveira CM, Ulbig M, Haritoglou C.

Purpose: To evaluate the influence of a ranibizumab treatment on microaneurysm (MA) turnover in diabetic retinopathy.

Methods: Sixty-nine eyes were included in this retrospective study. We compared a group of 33 eyes with ranibizumab treatment for diabetic macular edema to 36 eyes with nonproliferative diabetic retinopathy only. Nonmydriatic ultra-widefield scanning laser ophthalmoscopy (Optomap) images were obtained at a mean 4.76 ± 1.69 days prior to the first ranibizumab injection (baseline) and again 35.94 ± 2.44 days after the third consecutive injection in a 4-week interval. In untreated controls, images were obtained at baseline and 97.81 ± 3.16 days thereafter. Images were analyzed using the RetmarkerDR software (Critical Health SA, Coimbra, Portugal), and the turnover of MAs was documented and analyzed. Thereafter, MA turnover was correlated with central retinal thickness (CRT) as assessed by OCT.

Results: At baseline, patients in the treatment group had 5.64 ± 0.75 MAs. One month after 3 ranibizumab injections, measured MAs decreased to 4.03 ± 0.66. In the untreated control group, the initial number of 3.36 ± 0.6 MAs remained almost unchanged over 3-4 months (2.89 ± 0.57 MAs). Dynamic analysis showed that after ranibizumab treatment 3.06 ± 0.5 new MAs appeared, while 5.09 ± 0.79 disappeared. In the control group, 2.11 ± 0.4 new MAs appeared and 2.61 ± 0.48 disappeared. MA turnover was significantly higher with ranibizumab compared to the control group (8.15 ± 1.14 vs. 4.72 ± 0.81, $p < 0.001$). Consistently, CRT decreased from 444 to 330 µm in the ranibizumab group, while there was no change in the control group (291 vs. 288 µm).

Conclusion: The treatment of macular edema using ranibizumab does not only reduce macular thickness, but also has an impact on the turnover of MAs in diabetic retinopathy. RetmarkerDR analysis showed that more pre-existent MAs disappeared than new MAs developed, and the absolute number of MAs also decreased.

PMID: 24662930 [PubMed - as supplied by publisher]

Ophthalmologica. 2014 Mar 22. [Epub ahead of print]

Progression of Myopic Maculopathy after Treatment of Choroidal Neovascularization.

Farinha CL, Baltar AS, Nunes SG, Figueira JP, Pires IA, Cachulo ML, Silva RM.

Purpose: To evaluate the long-term progression of myopic maculopathy and functional outcome after treatment of myopic choroidal neovascularization (CNV) with photodynamic therapy (PDT) and/or intravitreal ranibizumab (IVR).

Methods: Retrospective study with a cross-sectional evaluation. Eyes were assigned to 4 groups (PDT, IVR, PDT + IVR, dry myopic maculopathy) and evaluated with best-corrected visual acuity, color fundus photography and spectral-domain optical coherence tomography. Chorioretinal atrophy progression was quantified.

Results: Fifty-four eyes were included with a mean follow-up of 80.6 ± 28.0 months. The prevalence of diffuse, patchy and macular atrophy increased during the follow-up, in contrast with tessellated fundus, lacquer cracks and active CNV. Progression of macular atrophy was significant in the 3 treatment groups ($p < 0.05$) and predictive of visual acuity. It depended on age, degree of myopia and presence of staphyloma, but not on the type of treatment.

Conclusions: The long-term functional outcome of eyes with myopic CNV is more dependent on the progression of macular atrophy, and not on the type of treatment.

PMID: 24662778 [PubMed - as supplied by publisher]

Mediators Inflamm. 2014;2014:364143. doi: 10.1155/2014/364143. Epub 2014 Feb 10.

Five-month observation of persistent diabetic macular edema after intravitreal injection of ozurdex implant.

Zalewski D, Raczyńska D, Raczyńska K.

Aims: This retrospective analysis was aimed at evaluating the effectiveness of treatment of persistent diabetic macular edema with intravitreal injections of 0.7 mg dexamethasone implant Ozurdex. The study comprised three male patients (6 eyes).

Results: The average thickness of the retina at baseline was 632 μ m, the medial BCVA was 0.8 logMAR, and corrected intraocular pressure was 13.7 mmHg. The maximum decrease in mean retinal thickness was observed at four weeks following the treatment and was 365 μ m (-267 μ m) and visual acuity improved by an average of two lines and was 0.6 logMAR. The largest increase in mean retinal thickness to average of 528 μ m (+164 μ m) occurred at 16 weeks and the average BCVA was 0.614 lines BCVA logMAR. In one eye, there was a steroid cataract development after the third dose of dexamethasone implant of 0.7 mg.

Conclusions. The intravitreal dexamethasone implant treatment of patients with persistent diabetic macular edema in whom laser photocoagulation proved to be ineffective and as a result they required a monthly injection of anti-VEGF factors (Ranibizumab, Bevacizumab) may be a good alternative to extending the interval of injections. However, reinjections involve a high risk of developing poststeroid cataracts, which is not without significance in middle-aged patients.

PMID: 24659860 [PubMed - in process] PMCID: PMC3934699

Other treatment & diagnosis

Ophthalmology. 2014 Mar 21. pii: S0161-6420(14)00133-X. doi: 10.1016/j.ophtha.2014.02.005. [Epub ahead of print]

Low-Luminance Visual Acuity and Microperimetry in Age-Related Macular Degeneration.

Wu Z, Ayton LN, Guymer RH, Luu CD.

OBJECTIVE: To compare the effectiveness of low-luminance visual acuity (LLVA) and microperimetry as functional measures in early stages of age-related macular degeneration (AMD).

DESIGN: Prospective cross-sectional study.

PARTICIPANTS: One hundred seventy-nine participants with a clinical spectrum of non-neovascular AMD and 26 control participants.

METHODS: Best-corrected visual acuity (BVCA), LLVA, and microperimetric retinal sensitivity were measured on 1 eye of all participants. Low-luminance deficit (LLD) was calculated as the difference between LLVA and BCVA. The functional parameters were compared between 6 clinical severity groups (from controls to non-foveal geographic atrophy [GA]), and the relationships and magnitude of these

parameters were determined and compared.

MAIN OUTCOME MEASURES: Visual acuity parameters (BCVA, LLVA, and LLD) and central retinal sensitivity.

RESULTS: Best-corrected visual acuity, LLVA, and central retinal sensitivity were reduced significantly for all AMD clinical severity groups when compared with control participants ($P \leq 0.002$), except for those with drusen between 63 and 125 μm ($P \geq 0.107$). However, LLD was not significantly different from control participants in all groups ($P \geq 0.073$), except in the non-foveal GA group ($P = 0.008$). A significant positive relationship between central retinal sensitivity and LLD ($R = 0.613$; $P < 0.001$), but not BCVA, suggests that there is a trend for LLVA to detect a greater extent of functional deficit than BCVA in eyes with increasingly poorer retinal sensitivity. However, the results of the linear regression models estimated central retinal sensitivity to be 6.1, 3.7, and 5.1 standard deviations (SDs) less than normal by the time BCVA, LLVA, and LLD, respectively, were 2 SDs less than normal.

CONCLUSIONS: In early stages of AMD, LLVA did not detect a greater extent of functional deficit than BCVA when compared with control participants. Although there was a trend for LLVA to be more effective at detecting foveal deficits than BCVA in eyes with increasingly poorer retinal sensitivity, both visual acuity measures were much less sensitive compared with microperimetry.

PMID: 24661863 [PubMed - as supplied by publisher]

J Ophthalmol. 2014;2014:510285. Epub 2014 Jan 14.

Current Treatment Limitations in Age-Related Macular Degeneration and Future Approaches Based on Cell Therapy and Tissue Engineering.

Fernández-Robredo P, Sancho A, Johnen S, Recalde S, Gama N, Thumann G, Groll J, García-Layana A.

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness in the Western world. With an ageing population, it is anticipated that the number of AMD cases will increase dramatically, making a solution to this debilitating disease an urgent requirement for the socioeconomic future of the European Union and worldwide. The present paper reviews the limitations of the current therapies as well as the socioeconomic impact of the AMD. There is currently no cure available for AMD, and even palliative treatments are rare. Treatment options show several side effects, are of high cost, and only treat the consequence, not the cause of the pathology. For that reason, many options involving cell therapy mainly based on retinal and iris pigment epithelium cells as well as stem cells are being tested. Moreover, tissue engineering strategies to design and manufacture scaffolds to mimic Bruch's membrane are very diverse and under investigation. Both alternative therapies are aimed to prevent and/or cure AMD and are reviewed herein.

PMID: 24672707 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2014 Mar 21. doi: 10.1136/bjophthalmol-2013-304405. [Epub ahead of print]

Small retinal haemorrhages accompanied by macular soft drusen: prevalence, and funduscopic and angiographic characteristics.

Kim JH, Lee TG, Kim JW, Kim CG, Cho SW, Han JI.

PURPOSE: To investigate the prevalence and clinical significance of small retinal haemorrhages accompanied by macular soft drusen in exudative age-related macular degeneration (AMD).

METHODS: This observational case series included patients who had first been diagnosed with exudative AMD. Small retinal haemorrhages were defined as preretinal or intraretinal haemorrhages, no larger than half the disc diameter in size and located within 3000 μm of the fovea centre. If there was more than one haemorrhage, the entire affected area was less than two-thirds of the disc diameter. Macular soft drusen

was defined as the presence of soft drusen (≥125 μm in diameter) within the macular area. The presence of retinal angiomatous proliferation (RAP) was estimated based on the results of indocyanine green angiography (ICGA). The prevalence of reticular pseudodrusen was also estimated.

RESULTS: Among the 1921 eyes from 1604 patients who were newly diagnosed with exudative AMD during the 40 months prior to the study, 101 eyes (5.3%) from 79 patients presented with the fundus characteristics described above. ICGA images were available for 69 eyes. Among these eyes, 28 eyes (43.1%) and 25 eyes (38.5%) were found to have type 1 and 2 RAP, respectively. A chorioretinal anastomosis (type 3 RAP) was identified in 12 (18.5%) eyes. Reticular pseudodrusen were noted in 78 eyes (77.2%).

CONCLUSIONS: The presence of small retinal haemorrhages accompanied by macular soft drusen was highly predictive of RAP. The high prevalence of both soft drusen and reticular pseudodrusen in these eyes may suggest a profound decrease in choroidal perfusion in these eyes.

PMID: 24659351 [PubMed - as supplied by publisher]

Adv Exp Med Biol. 2014;801:323-9. doi: 10.1007/978-1-4614-3209-8_41.

Utilizing Stem Cell-Derived RPE Cells as A Therapeutic Intervention for Age-Related Macular Degeneration.

Westenskow PD, Kurihara T, Friedlander M.

PURPOSE: Degeneration or dysfunction of the retinal pigment epithelium (RPE) can induce secondary photoreceptor atrophy and catastrophic vision loss in patients with age-related macular degeneration (AMD). AMD is the leading cause of vision loss in the elderly in industrialized countries and no cure exists for the "dry" or atrophic form to date. However, recent pre-clinical data from several groups suggests that embryonic stem cell-derived RPE cell transplantation may prevent photoreceptor degeneration in animal models of RPE degeneration. Another approach may be to derive RPE cells from autologous induced pluripotent stem cells (iPSCs) reprogrammed from dermal tissue. However, the safety of this approach has been questioned on several levels. In this chapter we will summarize work reported by several groups, including our own, that clearly demonstrate that transplanted RPE cells can provide anatomical and functional photoreceptor rescue in animal models of retinal degeneration. We will also discuss some of the prevailing concerns and challenges associated with this technique.

PMID: 24664714 [PubMed - in process]

Adv Exp Med Biol. 2014;801:309-16. doi: 10.1007/978-1-4614-3209-8_39.

Measuring Cone Density in a Japanese Macaque (Macaca fuscata) Model of Age-Related Macular Degeneration with Commercially Available Adaptive Optics.

Pennesi ME, Garg AK, Feng S, Michaels KV, Smith TB, Fay JD, Weiss AR, Renner LM, Hurst S, McGill TJ, Cornea A, Rittenhouse KD, Sperling M, Fruebis J,

Neuringer M.

Abstract: The aim of this study was to assess the feasibility of using a commercially available high-resolution adaptive optics (AO) camera to image the cone mosaic in Japanese macaques (Macaca fuscata) with dominantly inherited drusen. The macaques examined develop drusen closely resembling those seen in humans with age-related macular degeneration (AMD). For each animal, we acquired and processed images from the AO camera, montaged the results into a composite image, applied custom cone-counting software to detect individual cone photoreceptors, and created a cone density map of the macular region. We conclude that flood-illuminated AO provides a promising method of visualizing the cone mosaic in nonhuman primates. Future studies will quantify the longitudinal change in the cone mosaic and its relationship to the severity of drusen in these animals.

PMID: 24664712 [PubMed - in process]

Adv Exp Med Biol. 2014;801:251-7. doi: 10.1007/978-1-4614-3209-8_32.

Inflammatory Biomarkers for AMD.

Stanton CM, Wright AF.

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness worldwide, affecting an estimated 50 million individuals aged over 65 years.Environmental and genetic risk-factors implicate chronic inflammation in the etiology of AMD, contributing to the formation of drusen, retinal pigment epithelial cell dysfunction and photoreceptor cell death. Consistent with a role for chronic inflammation in AMD pathogenesis, several inflammatory mediators, including complement components, chemokines and cytokines, are elevated at both the local and systemic levels in AMD patients. These mediators have diverse roles in the alternative complement pathway, including recruitment of inflammatory cells, activation of the inflammasome, promotion of neovascularisation and in the resolution of inflammation. The utility of inflammatory biomarkers in assessing individual risk and progression of the disease is controversial. However, understanding the role of these inflammatory mediators in AMD onset, progression and response to treatment may increase our knowledge of disease pathogenesis and provide novel therapeutic options in the future.

PMID: 24664705 [PubMed - in process]

Vision Res. 2014 Mar 20. pii: S0042-6989(14)00051-0. doi: 10.1016/j.visres.2014.03.004. [Epub ahead of print]

The contribution of central and peripheral vision in scene categorization: A study on people with central vision loss.

Thibaut M, Tran TH, Szaffarczyk S, Boucart M.

Abstract: Studies in normally sighted people suggest that scene recognition is based on global physical properties and can be accomplished by the low resolution of peripheral vision. We examine the contribution of peripheral and central vision in scene gist recognition in patients with central vision loss and age-matched controls. Twenty-one patients with neovascular age related macular degeneration (AMD), with a visual acuity lower than 20/50, and 15 age-matched normally sighted controls participated in a natural/urban scene categorization task. The stimuli were colored photographs of natural scenes presented randomly at one of five spatial locations of a computer screen: centre, top left, top right, bottom left and bottom right at 12° eccentricity. Sensitivity (d') and response times were recorded. Normally sighted people exhibited higher sensitivity and shorter response times when the scene was presented centrally than for peripheral pictures. Sensitivity was lower and response times were longer for people with AMD than for controls at all spatial location. In contrast to controls patients were not better for central than for peripheral pictures. The results of normally sighted controls indicate that scene categorization can be accomplished by the low resolution of peripheral vision but central vision remains more efficient than peripheral vision for scene gist recognition. People with central vision loss likely categorized scenes on the basis of low frequency information both in normal peripheral vision and in low acuity central vision.

PMID:24657253 [PubMed - as supplied by publisher]

Pathogenesis

Invest Ophthalmol Vis Sci. 2014 Mar 27. pii: iovs.13-13554v1. doi: 10.1167/iovs.13-13554. [Epub ahead of print]

Retinal Pigment Epithelial Cell Death by the Alternative Complement Cascade: Role of Membrane Regulatory Proteins, Calcium, PKC and Oxidative Stress.

Yang P, Baciu P, Parker Kerrigan B, Etheridge M, Sung E, Toimil BA, Berchuck JE, Jaffe GJ.

Purpose: Retinal pigment epithelial (RPE) cell death is an important feature of the advanced forms of age-related macular degeneration (AMD). Complement alternative pathway (AP) activation is associated with RPE cell death in AMD. In this study, we developed a new model to initiate AP activation on RPE cells and investigated the cellular mechanisms modulating AP activation-mediated RPE cell death.

Methods: An anti-RPE antibody was developed. ARPE-19 and donor RPE cells were primed with this antibody followed by stimulation with 6% C1q-depleted human serum (C1q-Dep) to activate AP. Complement activation was evaluated by flow cytometry and immunofluorescent staining. Cellular response to complement activation was examined by measurement of intracellular calcium and ATP release. Cell viability was assessed by Sytox® orange, tetrazolium salt and lactate dehydrogenase release assays.

Results: AP complement-mediated RPE cell death was associated with membrane attack complex formation and a rapid rise in intracellular calcium followed by release of ATP. Down-regulation of membrane complement regulatory proteins and PKC inhibition increased cell susceptibility to complement attack. Pre-treatment of RPE cells with either hydrogen peroxide or hydroquinone enhanced cell death. Chronic repetitive treatment of RPE cells with low levels of oxidants also enhanced complement-mediated cell death.

Conclusions: Activation of complement through the alternative pathway induces sub-lytic and lytic phases of complement attack on RPE cells, leading to cell death modulated by extracellular calcium, membrane complement regulatory proteins, and intracellular signaling mechanisms. Single-dose oxidant exposure and low-dose repetitive oxidant exposure rendered RPE cells more susceptible to complement-mediated death.

PMID: 24677108 [PubMed - as supplied by publisher]

Exp Eye Res. 2014 Mar 24. pii: S0014-4835(14)00074-8. doi: 10.1016/j.exer.2014.03.006. [Epub ahead of print]

Vaccination with a mutated variant of human Vascular Endothelial Growth Factor (VEGF) blocks VEGF-induced retinal neovascularization in a rabbit experimental model.

Morera Y, González R, Lamdan H, Pérez L, González Y, Agüero J, Castro J, Romero JC, Etchegoyen AY, Ayala M, Gavilondo JV.

Abstract: Vascular endothelial growth factor (VEGF) is a key driver of the neovascularization and vascular permeability that leads to the loss of visual acuity of eye diseases like wet age-related macular degeneration, diabetic macular oedema, and retinopathy of premature. Among the several anti-VEGF therapies under investigation for the treatment of neovascular eye diseases, our group has developed the vaccine candidate CIGB-247-V that uses a mutated form of human VEGF as antigen. In this work we evaluated if the vaccine could prevent or attenuate VEGF-induced retinal neovascularization in the course of a rabbit eye neovascularization model, based on direct intravitreal injection of human VEGF. Our experimental findings have shown that anti-VEGF IgG antibodies induced by the vaccine were available in the retina blood circulation, and could neutralize in situ the neovascularization effect of VEGF. CIGB-247-V vaccination proved to effectively reduce retinal neovascularization caused by intravitreal VEGF injection. Altogether, these results open the way for human studies of the vaccine in neovascular eye syndromes, and inform on the potential mechanisms involved in its effect.

PMID: 24675387 [PubMed - as supplied by publisher]

Gene Ther. 2014 Mar 27. doi: 10.1038/gt.2014.24. [Epub ahead of print]

AAV-mediated expression of human PRELP inhibits complement activation, choroidal neovascularization and deposition of membrane attack complex in mice.

Birke MT, Lipo E, Adhi M, Birke K, Kumar-Singh R.

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness among the elderly.

Approximately 50% of AMD patients have a polymorphism in the negative regulator of complement known as Factor H. Individuals homozygous for a Y402H polymorphism in Factor H have elevated levels of membrane attack complex (MAC) in their choroid and retinal pigment epithelium relative to individuals homozygous for the wild-type allele. An inability to form MAC due to a polymorphism in C9 is protective against the formation of choroidal neovascularization (CNV) in AMD patients. Hence, blocking MAC in AMD patients may be protective against CNV. Here we investigate the potential of human proline/arginine-rich end leucine-rich repeat protein (PRELP) as an inhibitor of complement-mediated damage when delivered via the subretinal route using an AAV2/8 vector. In a fluorescence-activated cell sorting (FACS) lysis assay, PRELP inhibited normal human serum-mediated lysis of Hepa-1c1c7 cells by 18.7%. Unexpectedly, PRELP enhanced the formation of tubes by human umbilical vein endothelial cells (HUVECs) by approximately 240%, but, when delivered via an AAV vector to the retina of mice, PRELP inhibited laser-induced CNV by 60%. PRELP reduced deposition of MAC in vivo by 25.5%. Our results have implications for the development of complement inhibitors as a therapy for AMD.

PMID: 24670995 [PubMed - as supplied by publisher]

Adv Exp Med Biol. 2014;801:805-11. doi: 10.1007/978-1-4614-3209-8_101.

Targeting the PI3K/Akt/mTOR Pathway in Ocular Neovascularization.

Sasore T, Reynolds AL, Kennedy BN.

Abstract: Ocular neovascularization, a common pathological feature of wet age-related macular degeneration (AMD), proliferative and diabetic retinopathy (PDR) leads to fluid and blood leakage, scar formation and ultimately blindness. Elucidation of vascular endothelial growth factor (VEGF) as a key mediator of angiogenesis led to clinically approved anti-VEGF agents. However, these drugs are associated with adverse side-effects, high costs and extensive clinical burden. The phosphatidylinositol-3-kinase (PI3K) pathway is an alternative therapeutic target in angiogenic diseases. The PI3K/Akt/mTOR pathway orchestrates an array of normal cellular processes, including growth, survival and angiogenesis. Here, we review the potential of targeting the PI3K pathway, to treat ocular neovascularization.

PMID: 24664774 [PubMed - in process]

Biochim Biophys Acta. 2014 Mar 22. pii: S0167-4889(14)00100-1. doi: 10.1016/j.bbamcr.2014.03.016. [Epub ahead of print]

p62 Provides Dual Cytoprotection Against Oxidative Stress in the Retinal Pigment Epithelium.

Wang L, Cano M, Handa JT.

Abstract: As a signaling hub, p62/sequestosome plays important roles in cell signaling and degradation of misfolded proteins. p62 has been implicated as an adaptor protein to mediate autophagic clearance of insoluble protein aggregates in age-related diseases, including age-related macular degeneration (AMD), which is characterized by dysfunction of the retinal pigment epithelium (RPE). Our previous studies have shown that cigarette smoke (CS) induces oxidative stress and inhibits the proteasome pathway in cultured human RPE cells, suggesting that p62-mediated autophagy may become the major route to remove impaired proteins under such circumstances. In the present studies, we found that all p62 mRNA variants are abundantly expressed and upregulated by CS induced stress in cultured human RPE cells, yet isoform1 is the major translated form. We also show that p62 silencing exacerbated the CS induced accumulation of damaged proteins, both by suppressing autophagy and by inhibiting the Nrf2 antioxidant response, which in turn, increased protein oxidation. These effects of CS and p62 reduction were further confirmed in mice exposed to CS. We found that over-expression of p62 isoform1, but not its S403A mutant, which lacks affinity for ubiquitinated proteins, reduced misfolded proteins, yet simultaneously promoted an Nrf2-mediated antioxidant response. Thus, p62 provides dual, reciprocal enhancing protection to RPE cells from environmental stress induced protein misfolding and aggregation, by facilitating autophagy and the Nrf2 mediated antioxidant response, which might be a potential therapeutic target against AMD.

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Adv Exp Med Biol. 2014;801:623-9. doi: 10.1007/978-1-4614-3209-8_78.

Sphingolipids in ocular inflammation.

Chan AY, Mann SN, Chen H, Stone DU, Carr DJ, Mandal NA.

Abstract: Sphingolipids are essential to cell membrane structure and the development and maintenance of neural tissues. The role of bioactive sphingolipids has been established in numerous cellular events, including cell survival, growth, and apoptosis. Ocular inflammatory and autoimmune diseases involve activation and migration of endothelial cells, neovascularization, and infiltration of immune cells into various tissues. Clinically, the impact and role of sphingolipid-mediated signaling is increasingly being appreciated in the pathogenesis and treatment of diseases ranging from multiple sclerosis to neovascularization in age-related macular degeneration and diabetic retinopathy. In this review, we discuss our current knowledge and understanding of sphingolipid metabolism and signaling associated with the pathogenesis of ocular diseases.

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Adv Exp Med Biol. 2014;801:435-40. doi: 10.1007/978-1-4614-3209-8_55.

The Complement Regulatory Protein CD59: Insights into Attenuation of Choroidal Neovascularization.

Schnabolk G, Tomlinson S, Rohrer B.

Abstract: Complement activation is associated with age-related macular degeneration (AMD), with the retinal pigment epithelium (RPE) being one of the main target tissues. In AMD, disease severity is correlated with the formation of the membrane attack complex (MAC), the terminal step in the complement cascade, as well as diminished RPE expression of CD59, a membrane-bound regulatory protein of MAC formation. This has prompted the search for therapeutic strategies based on MAC inhibition, and soluble forms of CD59 (sCD59) have been investigated in mouse laser-induced choroidal neovascularization, a model for "wet" AMD. Unlike membrane-bound CD59, sCD59 provides relatively poor cell protection from complement, and different strategies to increase sCD59 activity at the cell membrane level have been investigated. These include increasing the circulatory half-life of sCD59 by the addition of an Fc moiety; increasing the half-life of sCD59 in target tissues by modifying CD59 with a (non-specific) membrane-targeting domain; and by locally overexpressing sCD59 via adenoviral vectors. Finally, a different strategy currently under investigation employs complement receptor (CR)2-mediated targeting of CD59 exclusively to membranes under complement attack. CR2 recognizes long-lasting membrane-bound breakdown activation fragments of complement C3. CR2-CD59 may have greater therapeutic potential than other complement inhibitory approaches, since it can be administered either systemically or locally, it will bind specifically to membranes containing activated complement activation fragments, and dosing can be regulated. Hence, this strategy might offer opportunities for site-specific inhibition of complement in diseases with restricted sites of inflammation such as AMD.

PMID: 24664728 [PubMed - in process]

Adv Exp Med Biol. 2014;801:427-33. doi: 10.1007/978-1-4614-3209-8_54.

The relevance of chemokine signalling in modulating inherited and age-related retinal degenerations.

Luhmann UF, Robbie SJ, Bainbridge JW, Ali RR.

Abstract: Systemic monocytes, tissue resident macrophages, dendritic cells and microglia have specific roles in immune surveillance and maintenance of tissue homeostasis and are key regulator and effector cells of the local immune response to acute and chronic tissue injury.Two major signalling pathways that differentially define trafficking behaviour and activation of systemic and local myeloid cell populations in

response to exogenous and endogenous inflammatory stimuli are the Ccl2-Ccr2 and the Cx3cl1-Cx3cr1 chemokine pathways.Alterations in these pathways have been implicated in controlling myeloid cell activation during normal ageing and in age-related retinal degenerations, including age-related macular degeneration (AMD).We review the evidence for how altered chemokine signalling in acute and chronic inflammatory conditions regulate local and systemic myeloid cell responses in the retina and how this may contribute to or attenuate pathology in inherited and age-related retinal diseases. We discuss the role of environmental factors (e.g. light exposure) and the influence of genetic factors on the manifestation of pathology in experimental models and in human patients and how we envisage harnessing this knowledge for the development of targeted, more broadly applicable anti-inflammatory treatment strategies for a wide range of retinal degenerations.

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Adv Exp Med Biol. 2014;801:409-15. doi: 10.1007/978-1-4614-3209-8_52.

An overview of the involvement of interleukin-18 in degenerative retinopathies.

Campbell M, Doyle SL, Ozaki E, Kenna PF, Kiang AS, Humphries MM, Humphries P.

Abstract: Age-related macular degeneration (AMD) is the leading cause of central vision loss worldwide and while polymorphisms in genes associated with the immune system have been identified as risk factors for disease development, the underlying pathways and mechanisms involved in disease progression have remained unclear. In AMD, localised inflammatory responses related to particulate matter accumulation and subsequent "sterile" inflammation has recently gained considerable interest amongst basic researchers and clinicians alike. Typically, inflammatory responses in the human body are caused as a result of bacterial or viral infection, however in chronic conditions such as AMD, extracellular particulate matter such as drusen can be "sensed" by the NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome, culminating in the release of the two pro-inflammatory cytokines IL-1β and IL-18 in the delicate local tissue of the retina. Identification at the molecular level of mediators of the inflammatory response in AMD may yield novel therapeutic approaches to this common and often severe form of blindness. Here, we will describe the role of IL-18 in AMD and other forms of retinal disorders. We will outline some of the key functions of IL-18 as it pertains to maintaining tissue homeostasis in a healthy and degenerating/diseased retina.

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Adv Exp Med Biol. 2014;801:317-21. doi: 10.1007/978-1-4614-3209-8_40.

Nuclear receptors as potential therapeutic targets for age-related macular degeneration.

Malek G.

Abstract: Age-related macular degeneration (AMD) is the most important cause of blindness and visual impairment among the elderly. Nuclear receptors represent one of the largest families of transcription factors, with 48 present in the human genome. They are critical regulators and modulators of developmental and physiological processes and are both targets of drugs and chemicals of environmental significance. Many of the cellular processes regulated by nuclear receptors are disrupted in AMD. With this in mind, we recently created a nuclear receptor atlas of retinal pigment epithelial (RPE) cells, cells affected in AMD, highlighting the expression of all the nuclear receptors. The results of which provided scaffold to study individual receptors in aging and disease. This study led to several candidate receptors that have become the focus of detailed studies regarding their mechanistic role in the eye. One example of a nuclear receptor potentially relevant to AMD pathobiology is presented.

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Adv Exp Med Biol. 2014;801:283-9. doi: 10.1007/978-1-4614-3209-8_36.

Is age-related macular degeneration a microvascular disease?

Mullins RF, Khanna A, Schoo DP, Tucker BA, Sohn EH, Drack AV, Stone EM.

Abstract: Age-related macular degeneration (AMD) is a common, degenerative disease of the central retina affecting millions of elderly in the USA alone and many more worldwide. A better understanding of the pathophysiology of AMD will be essential for developing new treatments. In this review, we discuss the potential impact of complement complex deposition at the choriocapillaris of aging eyes and the relationship between choriocapillaris loss and drusen formation. We further propose a model that integrates genetic and anatomical findings in AMD and suggest the implications of these findings for future therapies.

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Adv Exp Med Biol. 2014;801:275-81. doi: 10.1007/978-1-4614-3209-8_35.

Hypoxia-Inducible Factor (HIF)/Vascular Endothelial Growth Factor (VEGF) Signaling in the Retina.

Kurihara T, Westenskow PD, Friedlander M.

Abstract: Over a span of two decades, it has become increasingly clear that vascular endothelial growth factor (VEGF) plays an important role in the pathogenesis of retinal diseases including age-related macular degeneration (AMD) and diabetic retinopathy (DR). Based on these observations, anti-VEGF therapies are being developed and approved for clinical use in the treatment of neovascular eye diseases. Hypoxia-inducible factors (HIFs) are transcriptional factors that are stabilized and activated under hypoxic conditions and induce expression of gene products, including VEGF, that are required for cell survival under hypoxia. Here we discuss recent findings from our lab and others that define roles of the HIF-VEGF axis in the retina.

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Adv Exp Med Biol. 2014;801:267-74. doi: 10.1007/978-1-4614-3209-8_34.

Should I Stay or Should I Go? Trafficking of Sub-Lytic MAC in the Retinal Pigment Epithelium.

Lakkaraju A, Toops KA, Xu J.

Abstract: Assembly of sub-lytic C5b-9 membrane attack complexes (MAC) on the plasma membrane of retinal pigment epithelial cells contributes to the pathogenesis of age-related macular degeneration. C5b-9 pores induce calcium influx, which activates signaling pathways that compromise cell function. Mechanisms that limit sub-lytic MAC activity include: cell surface complement regulatory proteins CD46, CD55, and CD59 that inhibit specific steps of MAC formation; elimination of assembled MAC by exocytosis of membrane vesicles or by endocytosis and subsequent lysosomal degradation; and rapid resealing of pores by the exocytosis of lysosomes. Aging in the post-mitotic retinal pigment epithelium is characterized by the accumulation of cellular debris called lipofuscin, which has also been associated with retinal diseases such as age-related macular degeneration. Lipofuscin has been shown to activate complement components both in vitro and in vivo, suggesting that it could contribute complement-mediated dysfunction in the retinal pigment epithelium. Here, we discuss emerging evidence that vesicular trafficking in the retinal pigment epithelium is critical for efficient removal of MAC from the cell surface and for limiting inflammation in the outer retina.

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Adv Exp Med Biol. 2014;801:259-65. doi: 10.1007/978-1-4614-3209-8_33.

Oxidized Low-Density-Lipoprotein-Induced Injury in Retinal Pigment Epithelium Alters Expression of the Membrane Complement Regulatory Factors CD46 and CD59 through Exosomal and Apoptotic Bleb Release.

Ebrahimi KB, Fijalkowski N, Cano M, Handa JT.

Abstract: Genetic and immunohistochemical studies have identified the alternative complement pathway as an important component of age-related macular degeneration (AMD). The objective of this chapter is to review the impact of complement regulators on complement activation in the macula as it relates to AMD. Our laboratory and other investigators have identified CD46 and CD59 as important retinal pigment epithelium (RPE) cell membrane complement regulators, which are decreased in AMD. Using oxidized low-density lipoproteins (oxLDLs), which are found in Bruch's membrane in AMD, we found that CD46 and CD59 were decreased in RPE cells in part, by their release in exosomes and apoptotic particles. The release of complement regulators could potentially impair complement regulation on RPE cells and contribute to lesion formation in the outer retina and Bruch's membrane during the development of AMD.

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Adv Exp Med Biol. 2014;801:229-35. doi: 10.1007/978-1-4614-3209-8_30.

Inflammation in age-related macular degeneration.

Ozaki E, Campbell M, Kiang AS, Humphries M, Doyle SL, Humphries P.

Abstract:Age-related macular degeneration (AMD) is the leading cause of legal blindness in elderly individuals in the developed world, affecting 30-50 million people worldwide. AMD primarily affects the macular region of the retina that is responsible for the majority of central, color and daytime vision. The presence of drusen, extracellular protein aggregates that accumulate under the retinal pigment epithelium (RPE), is a major pathological hallmark in the early stages of the disease. The end stage 'dry' and 'wet' forms of the disease culminate in vision loss and are characterized by focal degeneration of the RPE and cone photoreceptors, and choroidal neovascularization (CNV), respectively. Being a multifactorial and genetically heterogeneous disease, the pathophysiology of AMD remains unclear, yet, there is ample evidence supporting immunological and inflammatory processes. Here, we review the recent literature implicating some of these immune processes in human AMD and in animal models.

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Adv Exp Med Biol. 2014;801:221-7. doi: 10.1007/978-1-4614-3209-8_29.

Prolonged SRC kinase activation, a mechanism to turn transient, sublytic complement activation into a sustained pathological condition in retinal pigment epithelium cells.

Rohrer B, Kunchithapautham K, Genewsky A, Strauß O.

Abstract: Age-related macular degeneration (AMD) is a slowly progressing multifactorial disease involving genetic abnormalities and environmental insults. Genetic studies have demonstrated that polymorphisms in different complement proteins increase the risk for developing AMD. Previously, we have shown that in retinal pigment epithelium (RPE) monolayers, exposure to oxidative stress reduced complement inhibition on the cell surface, with the resulting increase in complement activation leading to vascular endothelial growth factor (VEGF) release and VEGF-receptor-2-mediated disruption of the monolayer barrier function. Complement activation was found to be sublytic and transient and require the assembly of the membrane attack complex (MAC). Here, we asked how this transient, sublytic complement activation could trigger long -term pathological changes in RPE cells. The initial activation of the L-type voltage-gated calcium channels was followed by calcium influx and activation of several kinases. While Erk/Ras activation was found to be transient, Src kinase phosphorylation was sustained. We have shown previously that Src kinase controls

VEGF release from RPE cells by altering the activity of the L-type channel. We propose that the prolonged Src kinase activation, and its resulting effects on membrane depolarization and calcium influx, leads to sustained VEGF secretion. In addition, the previously shown effect of the autocrine positive feedback loop in RPE cells, involving VEGF-induced VEGF production and secretion via VEGFR-2 receptors, will augment and prolong the effects of sublytic complement activation. In summary, identification of the links between oxidative stress, chronic, low-grade activation of the complement system, and elevated VEGF expression and secretion might offer opportunities to selectively inhibit pathological VEGF release only.

PMID: 24664702 [PubMed - in process]

Adv Exp Med Biol. 2014;801:213-9. doi: 10.1007/978-1-4614-3209-8_28.

The Role of Complement Dysregulation in AMD Mouse Models.

Ding JD, Kelly U, Groelle M, Christenbury JG, Zhang W, Bowes Rickman C.

Abstract: Variations in several complement genes are now known to be significant risk factors for the development of age-related macular degeneration (AMD). Despite dramatic effects on disease susceptibility, the underlying mechanisms by which common polymorphisms in complement proteins alter disease risk have remained unclear. Genetically modified mice in which the activity of the complement has been altered are available and can be used to investigate the role of complement in the pathogenesis of AMD. In this mini review, we will discuss some existing complement models of AMD and our efforts to develop and characterize the ocular phenotype in a variety of mice in which complement is either chronically activated or inhibited. A spectrum of complement dysregulation was modeled on the APOE4 AMD mouse model by crossing these mice to complement factor H knockout (cfh-/-) mice to test the impact of excess complement activation, and by crossing them to soluble-complement-receptor-1-related protein y (sCrry) mice, in which sCrry acts as a potent inhibitor of mouse complement acting in a manner similar to CFH. In addition, we have also generated humanized CFH mice expressing normal and risk variants of CFH.

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Adv Exp Med Biol. 2014;801:207-12. doi: 10.1007/978-1-4614-3209-8_27.

Microglia in the aging retina.

Karlstetter M, Langmann T.

Abstract: In the healthy retina, microglial cells represent a self-renewing population of innate immune cells, which constantly survey their microenvironment. Equipped with receptors, a microglial cell detects subtle cellular damage and rapidly responds with activation, migration, and increased phagocytic activity. While the involvement of microglial cells has been well characterized in monogenic retinal disorders, it is still unclear how they contribute to the onset of retinal aging disorders including age-related macular degeneration (AMD). There is evidence, that microglial activation is not solely a secondary manifestation of retinal tissue damage in age-related disorders. Thus, work in the aging rodent and human retina suggests that long-lived and genetically predisposed microglia transform into a dystrophic state, with loss of neuroprotective functions. In this concept, malfunction of aging microglia can trigger a chronic low-grade inflammatory environment that favors the onset and progression of retinal degeneration.

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Adv Exp Med Biol. 2014;801:199-205. doi: 10.1007/978-1-4614-3209-8_26.

The role of monocytes and macrophages in age-related macular degeneration.

Grunin M, Hagbi-Levi S, Chowers I.

Abstract: White blood cells, particularly monocytes and their descendants, macrophages, have been implicated in age-related macular degeneration (AMD) pathology. In this minireview, we describe the current knowledge of monocyte and macrophage involvement in AMD. Chemokine receptors present on these cells such as CCR1, CCR2, and CX3CR1, and their roles in monocyte/macrophage recruitment to sites of injury and inflammation in the context of AMD will be reviewed. Mice models for perturbation of chemokine receptors that recapitulate some of the features of AMD are also described. The body of evidence from human and rodent studies at this point in time suggests that monocyte and macrophages may modulate the course of AMD.

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Adv Exp Med Biol. 2014;801:193-8. doi: 10.1007/978-1-4614-3209-8_25.

Molecular pathology of macrophages and interleukin-17 in age-related macular degeneration.

Chan CC, Ardeljan D.

Abstract: The pathology of age-related macular degeneration (AMD) is characterized by degeneration of photoreceptors and retinal pigment epithelial cells as well as by changes of choroidal capillaries in the macula. Although AMD is not a typical uveitis, there is a consistence and an imbalance of ocular para-inflammation. Ocular inflammation, particularly in the macula, plays a critical role in AMD pathogenesis. The inflammatory and immune-related elements involved in AMD include inflammatory and related cells as well as the secreted molecules and factors from these cells. Innate immune system elements such as macrophages and cytokines play an important role in AMD pathology and pathogenesis. This chapter reviews the observed deviation in macrophage plasticity and the elevated expression of interleukin-17 in AMD eyes while discussing potential contributions to AMD pathogenesis. Targeting of these specific inflammatory pathways and molecules at appropriate times should be explored and may become promising novel adjunct agents to AMD therapy.

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Adv Exp Med Biol. 2014;801:113-9. doi: 10.1007/978-1-4614-3209-8_15.

The role of bestrophin-1 in intracellular ca(2+) signaling.

Strauß O, Müller C, Reichhart N, Tamm ER, Gomez NM.

Abstract: Mutations in the BEST1 gene lead to a variety of retinal degenerations, among them Best's vitelliforme macular degeneration. To clarify the mechanism of the disease, the understanding of the function of BEST1 gene product, bestrophin-1, is mandatory. In overexpression studies bestrophin-1 appeared to function as a Ca(2+)-dependent Cl channel. On the other hand, bestrophin-1 is able to participate in intracellular Ca(2+) signaling. Endogenously expressed bestrophin-1 largely localized to the cytosolic compartment close to the basolateral membrane of the retinal pigment epithelium (RPE) as it can be shown using differential centrifugation, immunohistochemistry, and transmission electron microscopy. To elucidate a cytosolic function of bestrophin-1, we explored the store-operated Ca(2+) entry in short-time cultured porcine RPE cells. Depletion of cytosolic Ca(2+)stores by SERCA inhibition led to activation of Orai -1 Ca(2+) channels. This resulted in an influx of extracellular Ca(2+) into the cell which was reduced when bestrophin-1 expression was knocked down using siRNA techniques. Quantification of Ca(2+) which can be released from cytosolic Ca(2+) stores revealed that after reduction of bestrophin-1 expression less Ca(2+) is stored in ER Ca(2+) stores. Thus, bestrophin-1 functions as an intracellular Cl channel which helps to accumulate and to release Ca(2+) from stores by conducting the counterion for Ca(2+).

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Adv Exp Med Biol. 2014;801:105-11. doi: 10.1007/978-1-4614-3209-8_14.

Rescue of compromised lysosomes enhances degradation of photoreceptor outer segments and reduces lipofuscin-like autofluorescence in retinal pigmented epithelial cells.

Guha S, Liu J, Baltazar G, Laties AM, Mitchell CH.

Abstract: Healthful cell maintenance requires the efficient degradative processing and removal of waste material. Retinal pigmented epithelial (RPE) cells have the onerous task of degrading both internal cellular debris generated through autophagy as well as phagocytosed photoreceptor outer segments. We propose that the inadequate processing material with the resulting accumulation of cellular waste contributes to the downstream pathologies characterized as age-related macular degeneration (AMD). The lysosomal enzymes responsible for clearance function optimally over a narrow range of acidic pH values; elevation of lysosomal pH by compounds like chloroquine or A2E can impair degradative enzyme activity and lead to a lipofuscin-like autofluorescence. Restoring acidity to the lysosomes of RPE cells can enhance activity of multiple degradative enzymes and is therefore a logical target in early AMD. We have identified several approaches to reacidify lysosomes of compromised RPE cells; stimulation of beta-adrenergic, A2A adenosine and D5 dopamine receptors each lowers lysosomal pH and improves degradation of outer segments. Activation of the CFTR chloride channel also reacidifies lysosomes and increases degradation. These approaches also restore the lysosomal pH of RPE cells from aged ABCA4(-/-) mice with chronically high levels of A2E, suggesting that functional signaling pathways to reacidify lysosomes are retained in aged cells like those in patients with AMD. Acidic nanoparticles transported to RPE lysosomes also lower pH and improve degradation of outer segments. In summary, the ability of diverse approaches to lower lysosomal pH and enhance outer segment degradation support the proposal that lysosomal acidification can prevent the accumulation of lipofuscin-like material in RPE cells.

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Adv Exp Med Biol. 2014;801:97-103. doi: 10.1007/978-1-4614-3209-8_13.

Vacuolar ATPases and their role in vision.

Shine L, Kilty C, Gross J, Kennedy B.

Abstract: Vacuolar ATPases (v-ATPases) hydrolyze adenosine triphospate (ATP) to pump protons across cell membranes. Mutations in v-ATPase subunits are implicated in three human disorders: distal renal tubular acidosis, osteopetrosis, and cutis laxa type II. In the eye, the role of v-ATPases is only emerging. Mutations in v-ATPase subunits are not linked to human blindness, but altered proton pump function may underlie ocular pathologies. For example, inhibition of v-ATPase by A2E may accentuate age-related macular degeneration (AMD). In animal models, v-ATPase mutations perturb the retinal pigment epithelium (RPE) and photoreceptor outer segment (OS) phagocytosis, an event linked to retinal degeneration. As the RPE plays essential roles in eye development and vision, the study of v-ATPase-induced RPE dysfunction may improve our understanding of RPE diseases.

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Adv Exp Med Biol. 2014;801:77-83. doi: 10.1007/978-1-4614-3209-8_10.

Animal Models, in "The Quest to Decipher RPE Phagocytosis".

Nandrot EF.

Abstract: Renewal and elimination of aged photoreceptor outer segment (POS) tips by cells from the retinal pigment epithelial (RPE) is a daily rhythmic process that is crucial for long-term vision. Anomalies can arise during any of the sequential steps required for completion of this phagocytic function, from POS recognition to complete digestion of POS components. During the past 15 years, many animal models helped us characterize the molecular machinery implicated in RPE phagocytosis as well as understand associated

defects leading to various retinal pathologies. Depending on which part of the machinery is flawed, phenotypes can either appear early in life, such as retinitis pigmentosa or Usher syndrome, or develop with aging of the individual, like age-related macular degeneration, affecting first either the peripheral or the central retina. This chapter describes mouse and rat models related to defective phagocytosis, and how they have been a tremendous help for us to comprehend RPE phagocytosis, its rhythm, and its failures.

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Adv Exp Med Biol. 2014;801:23-30. doi: 10.1007/978-1-4614-3209-8_4.

Glutathione S-Transferase Pi Isoform (GSTP1) Expression in Murine Retina Increases with Developmental Maturity.

Lee WH, Joshi P, Wen R.

BACKGROUND AND AIMS: Glutathione S-transferase pi isoform (GSTP1) is an intracellular detoxification enzyme that catalyzes reduction of chemically reactive electrophiles and is a zeaxanthin-binding protein in the human macula. We have previously demonstrated that GSTP1 levels are decreased in human age-related macular degeneration (AMD) retina compared to normal controls (Joshi et al., Invest Ophthalmol Vis Sci, e-abstract, 2009). We also showed that GSTP1 levels parallel survival of human retinal pigment epithelial (RPE) cells exposed to ultraviolet (UV) light, and GSTP1 over-expression protects them against UV light damage (Joshi et al., Invest Ophthalmol Vis Sci, e-abstract, 2010). In the present work, we determined the developmental time course of GSTP1 expression in murine retina and in response to light challenge.

METHODS: Eyes from BALB/c mice at postnatal day 20, 1 month, and 2 months of age were prepared for retinal protein extraction and cryo sectioning, and GSTP1 levels in the retina were analyzed by Western blot and immunohistochemistry (IHC). Another group of BALB/c mice with the same age ranges was exposed to 1000 lx of white fluorescent light for 24 h, and their retinas were analyzed for GSTP1 expression by Western blot and IHC in a similar manner.

RESULTS: GSTP1 levels in the murine retina increased in ascending order from postnatal day 20, 1 month, and 2 months of age. Moreover, GSTP1 expression in murine retina at postnatal day 20, 1 month, and 2 months of age increased in response to brief light exposure compared to age-matched controls under normal condition.

CONCLUSIONS: GSTP1 expression in retina increases with developmental age in mice and accompanies murine retinal maturation. Brief exposure to light induces GSTP1 expression in the murine retina across various developmental ages. GSTP1 induction may be a protective response to light-induced oxidative damage in the murine retina.

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Ocul Immunol Inflamm. 2014 Mar 21. [Epub ahead of print]

Elevated Plasma Pentraxin3 Levels and Its Association with Neovascular Age-related Macular Degeneration.

Min JK, Kim J, Woo JM.

Abstract Purpose: To evaluate pentraxin3 (PTX3) levels in patients with neovascular age-related macular degeneration (N-ARMD) and to investigate its role as a predictive biomarker.

Methods: Thirty individuals with N-ARMD and 30 controls without N-ARMD were studied. Plasma concentrations of C-reactive protein (CRP) and PTX3 were measured in frozen samples using an enzyme-linked immunosorbent assay kit.

Results: PTX3 concentration was 1341 ± 625 pg/mL (mean ± standard deviation) in N-ARMD patients, which was significantly higher than in control subjects (887 ± 478, p = 0.003). The mean CRP level was also significantly higher in N-ARMD (2121 ± 2300) than in control (748 ± 618, p = 0.004). Pearson's correlation analysis showed a significant positive correlation between PTX3 and CRP (r = 0.407, p = 0.002).

Conclusions: Our data support the role of chronic inflammation in the development of ARMD. They also show PTX3 may contribute to efforts to understand pathogenesis of N-ARMD.

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Epidemiology

Ophthalmology. 2014 Mar 21. pii: S0161-6420(14)00109-2. doi: 10.1016/j.ophtha.2014.02.004. [Epub ahead of print]

Prevalence, Racial Variations, and Risk Factors of Age-Related Macular Degeneration in Singaporean Chinese, Indians, and Malays.

Cheung CM, Li X, Cheng CY, Zheng Y, Mitchell P, Wang JJ, Wong TY.

OBJECTIVE: To describe the prevalence and risk factors for age-related macular degeneration (AMD) in a multiethnic Asian cohort of Chinese, Malay, and Indian persons.

DESIGN: Population-based cross-sectional study.

PARTICIPANTS: A total of 10 033 persons (3280 Malay, 3400 Indian, and 3353 Chinese; response rate, 75%) 40 years of age or older residing in Singapore.

METHODS: We performed comprehensive systemic and ocular examinations, retinal photography, and laboratory investigations for all participants. We graded early and late AMD signs from retinal photographs using the modified Wisconsin AMD grading scale. We calculated the age-standardized prevalence of AMD using the 2010 Singapore adult population and analyzed risk factors for AMD using logistic regression models.

MAIN OUTCOME MEASURES: Early and late AMD.

RESULTS: Of the 9799 participants with gradable photographs, 588 had early AMD and 60 had late AMD. The age-standardized prevalence was 5.1% (95% confidence interval [CI], 4.6-5.5) for early AMD and 0.5% (95% CI, 0.4-0.6) for late AMD. The prevalence of early AMD was similar between Chinese (5.7%) and Indian (4.5%; P = 0.27) persons and lower in Malays (3.5%; P = 0.002 compared with Chinese; P = 0.09 compared with Indians); in contrast, the prevalence for late AMD was similar across ethnic groups (Chinese, 0.6%; Indian, 0.3%; and Malay, 0.3%; P = 0.20). Risk factors for early AMD were older age (odds ratio [OR], 1.40 per 5-year increase in age; 95% CI, 1.33-1.47), male gender (OR, 1.81; 95% CI, 1.43-2.29), hypertension (OR, 1.28; 95% CI, 1.02-1.61), and hyperopic refraction (OR, 1.17 per 1-diopter increase in spherical equivalent; 95% CI, 1.11-1.24). Risk factors for late AMD include older age (OR, 1.87 per 5-year increase in age; 95% CI, 1.54-2.19), smoking more than 5 packs per week (OR, 3.63; 95% CI, 1.34-9.80), and presence of chronic kidney disease (OR, 2.17; 95% CI, 1.22-3.88).

CONCLUSIONS: Early AMD is more common in Chinese and Indians than in Malays, but there were no racial variations in the prevalence of late AMD.

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Prevalence and causes of vision loss in high-income countries and in Eastern and Central Europe: 1990-2010.

Bourne RR, Jonas JB, Flaxman SR, Keeffe J, Leasher J, Naidoo K, Parodi MB, Pesudovs K, Price H, White RA, Wong TY, Resnikoff S, Taylor HR; on behalf of the Vision Loss Expert Group of the Global Burden of Disease Study.

BACKGROUND: To assess prevalence and causes of blindness and vision impairment in high-income regions and in Central/Eastern Europe in 1990 and 2010.

METHODS: Based on a systematic review of medical literature, prevalence of moderate and severe vision impairment (MSVI; presenting visual acuity <6/18 but ≥3/60 in the better eye) and blindness (presenting visual acuity <3/60) was estimated for 1990 and 2010.

RESULTS: Age-standardised prevalence of blindness and MSVI decreased from 0.2% to 0.1% (3.314 million to 2.736 million people) and from 1.6% to 1.0% (25.362 million to 22.176 million), respectively. Women were generally more affected than men. Cataract was the most frequent cause of blindness in all subregions in 1990, but macular degeneration and uncorrected refractive error became the most frequent causes of blindness in 2010 in all high-income countries, except for Eastern/Central Europe, where cataract remained the leading cause. Glaucoma and diabetic retinopathy were fourth and fifth most common causes for blindness for all regions at both times. Uncorrected refractive error, followed by cataract, macular degeneration, glaucoma and diabetic retinopathy, was the most common cause for MSVI in 1990 and 2010.

CONCLUSIONS: In highly developed countries, prevalence of blindness and MSVI has been reduced by 50% and 38%, respectively, and the number of blind people and people with MSVI decreased by 17.4% and 12.6%, respectively, even with the increasing number of older people in the population. In high-income countries, macular degeneration has become the most important cause of blindness, but uncorrected refractive errors continue to be the leading cause of MSVI.

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Measures of Body Shape and Adiposity as Related to Incidence of Age-related Eye Diseases: Observations from the Beaver Dam Eye Study.

Howard KP, Klein BE, Lee KE, Klein R.

Purpose: To examine the effect of obesity on the incidence of age-related eye disease.

Methods: Participants of the Beaver Dam Eye Study were examined every five years over a twenty-year period (1988-1990 through 2008-2010). Lens and fundus photographs were used to evaluate presence and severity of cataract and macular degeneration. Height and weight were measured at all examinations. Waist and hip circumference were measured at all examinations beginning at the first follow-up (1993-1995). Models of ocular outcomes over 15 years were stratified by sex and smoking status.

Results: Overall, 2641 participants contributed 5567 person-visits to 15-year incidence analysis. Female non-smokers had increased risk of late age-related macular degeneration (AMD) associated with higher body mass index (BMI) (hazard ratio (HR) per 2.5 kg/m² 1.31, 95% confidence interval (CI) 1.15, 1.50, p<0.001), waist to hip ratio (WHR) (HR per 0.1 cm/cm 1.95, 95% CI 1.33, 2.86, p<0.001), waist circumference (WC) (HR per 5 cm 1.21, 95% CI 1.10, 1.34, p<.001), and waist to height ratio (WHtR) (HR per 0.1 cm/cm 1.74, 95% CI 1.31, 2.31, p<.001). Increased BMI was also associated with early AMD in female non-smokers (HR 1.10, 95% CI 1.02, 1.19, p=0.02). Conclusions Female non-smokers had an increased risk of late AMD associated with increasing measures of obesity and increased risk of early AMD associated with increasing BMI.

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Genetics

PLoS One. 2014 Mar 27;9(3):e93459. doi: 10.1371/journal.pone.0093459. eCollection 2014.

Impact of the Common Genetic Associations of Age-Related Macular Degeneration upon Systemic Complement Component C3d Levels.

Ristau T, Paun C, Ersoy L, Hahn M, Lechanteur Y, Hoyng C, de Jong EK, Daha MR, Kirchhof B, den Hollander AI, Fauser S.

Abstract: Age-related macular degeneration (AMD) is a common condition that leads to severe vision loss and dysregulation of the complement system is thought to be associated with the disease. To investigate associations of polymorphisms in AMD susceptibility genes with systemic complement activation, 2655 individuals were genotyped for 32 single nucleotide polymorphisms (SNPs) in or near 23 AMD associated risk genes. Component 3 (C3) and its catabolic fragment C3d were measured in serum and AMD staging was performed using multimodal imaging. The C3d/C3 ratio was calculated and associations with environmental factors, SNPs and various haplotypes of complement factor H (CFH) genes and complement factor B (CFB) genes were analyzed. Linear models were built to measure the influence of genetic variants on the C3d/C3 ratio. The study cohort included 1387 patients with AMD and 1268 controls. Higher C3d/C3 ratios were found for current smoker (p=0.002), higher age (p=1.56×10-7), AMD phenotype (p=1.15×10-11) and the two SNPs in the C3 gene rs6795735 (p=0.04) and rs2230199 (p=0.04). Lower C3d/C3 ratios were found for diabetes (p=2.87×10-6), higher body mass index (p=1.00×10-13), the SNPs rs1410996 (p=0.0001), rs800292 (p=0.003), rs12144939 (p=4.60×10-6) in CFH, rs4151667 (p=1.01×10-5) in CFB and individual haplotypes in CFH and CFB. The linear model revealed a corrected R-square of 0.063 including age, smoking status, gender, and genetic polymorphisms explaining 6.3% of the C3d/C3 ratio. After adding the AMD status the corrected R-square was 0.067. In conclusion, none of the evaluated genetic polymorphisms showed an association with increased systemic complement activation apart from two SNPs in the C3 gene. Major genetic and non-genetic factors for AMD were not associated with systemic complement activation.

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Adv Exp Med Biol. 2014;801:719-24. doi: 10.1007/978-1-4614-3209-8_90.

Gene Therapy for Stargardt Disease Associated with ABCA4 Gene.

Han Z, Conley SM, Naash MI.

Abstract: Mutations in the photoreceptor-specific flippase ABCA4 lead to accumulation of the toxic bisretinoid A2E, resulting in atrophy of the retinal pigment epithelium (RPE) and death of the photoreceptor cells. Many blinding diseases are associated with these mutations including Stargardt's disease (STGD1), cone-rod dystrophy, retinitis pigmentosa (RP), and increased susceptibility to age-related macular degeneration. There are no curative treatments for any of these dsystrophies. While the monogenic nature of many of these conditions makes them amenable to treatment with gene therapy, the ABCA4 cDNA is 6.8 kb and is thus too large for the AAV vectors which have been most successful for other ocular genes. Here we review approaches to ABCA4 gene therapy including treatment with novel AAV vectors, lentiviral vectors, and non-viral compacted DNA nanoparticles. Lentiviral and compacted DNA nanoparticles in particular have a large capacity and have been successful in improving disease phenotypes in the Abca4 (-/-) murine model. Excitingly, two Phase I/IIa clinical trials are underway to treat patients with ABCA4-associated Startgardt's disease (STGD1). As a result of the development of these novel technologies, effective therapies for ABCA4-associated diseases may finally be within reach.

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Diagn Pathol. 2014 Mar 25;9(1):73. [Epub ahead of print]

Association study of newly identified age-related macular degeneration susceptible loci SOD2, MBP, and C8orf42 in Han Chinese population.

Kan M, Liu F, Weng X, Ye J, Wang T, Xu M, He L, Liu Y.

Abstract: A recent genome-wide association study has reported three newly identified susceptible loci (rs2842992 near the gene SOD2, rs1789110 near the gene MBP and rs722782 near the gene C8orf42) to be associated with the geographic atrophy subtype of age-related macular degeneration in European-descent population. We investigated the correlation between these variants and advanced age-related macular degeneration for the first time in a Han Chinese cohort; however, no evidence supports these previously identified loci contribute to advanced age-related macular degeneration susceptibility in Chinese population.

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Clin Genet. 2014 Mar 25. doi: 10.1111/cge.12389. [Epub ahead of print]

Personalized ophthalmology.

Porter LF, Black GC.

Abstract: Ophthalmology has been an early adopter of personalized medicine. Drawing on genomic advances to improve molecular diagnosis, such as next-generation sequencing, and basic and translational research to develop novel therapies, application of genetic technologies in ophthalmology now heralds development of gene replacement therapies for some inherited monogenic eye diseases. It also promises to alter prediction, diagnosis and management of the complex disease age-related macular degeneration. Personalized ophthalmology is underpinned by an understanding of the molecular basis of eye disease. Two important areas of focus are required for adoption of personalized approaches: disease stratification and individualization. Disease stratification relies on phenotypic and genetic assessment leading to molecular diagnosis; individualization encompasses all aspects of patient management from optimized genetic counseling and conventional therapies to trials of novel DNA-based therapies. This review discusses the clinical implications of these twin strategies. Advantages and implications of genetic testing for patients with inherited eye diseases, choice of molecular diagnostic modality, drivers for adoption of personalized ophthalmology, service planning implications, ethical considerations and future challenges are considered. Indeed, whilst many difficulties remain, personalized ophthalmology truly has the potential to revolutionize the specialty.

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Adv Exp Med Biol. 2014;801:291-300. doi: 10.1007/978-1-4614-3209-8_37.

Genetic risk models in age-related macular degeneration.

Grassmann F, Heid IM, Weber BH.

Abstract: Late-stage age-related macular degeneration (AMD) is a common sight-threatening disease of the central retina affecting approximately 1 in 30 Caucasians. Besides age and smoking, common genetic variants from at least 19 gene loci have reproducibly been associated with AMD likely explaining a large proportion of disease. Based on the current knowledge, several models were calculated to predict disease risk each with its own strength and weakness. Here, we review and compare published genetic risk models for AMD with or without additionally accounting for non-genetic factors.

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Adv Exp Med Biol. 2014;801:237-50. doi: 10.1007/978-1-4614-3209-8_31.

Impairment of the Ubiquitin-Proteasome Pathway in RPE Alters the Expression of Inflammation Related Genes.

Liu Z, Qin T, Zhou J, Taylor A, Sparrow JR, Shang F.

Abstract: The ubiquitin-proteasome pathway (UPP) plays an important role in regulating gene expression. Retinal pigment epithelial cells (RPE) are a major source of ocular inflammatory cytokines. In this work we determined the relationship between impairment of the UPP and expression of inflammation-related factors. The UPP could be impaired by oxidative stress or chemical inhibition. Impairment of the UPP in RPE increased the expression of several inflammatory cytokines, such as IL-6 and IL-8. However, the expression of monocyte chemoattractant protein-1 (MCP-1) and complement factor H (CFH) and was reduced upon impairment of the UPP. These data suggest that impairment of the UPP in RPE may be one of the causes of retinal inflammation and abnormal functions of monocyte and the complement system during the pathogenesis of age-related macular degeneration.

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Diet & lifestyle

PLoS One. 2014 Mar 27;9(3):e92659. doi: 10.1371/journal.pone.0092659. eCollection 2014.

The effect of modified eggs and an egg-yolk based beverage on serum lutein and zeaxanthin concentrations and macular pigment optical density: results from a randomized trial.

Kelly ER, Plat J, Haenen GR, Kijlstra A, Berendschot TT.

Abstract: Increasing evidence suggests a beneficial effect of lutein and zeaxanthin on the progression of age-related macular degeneration. The aim of this study was to investigate the effect of lutein or zeaxanthin enriched eggs or a lutein enriched egg-yolk based buttermilk beverage on serum lutein and zeaxanthin concentrations and macular pigment levels. Naturally enriched eggs were made by increasing the levels of the xanthophylls lutein and zeaxanthin in the feed given to laying hens. One hundred healthy volunteers were recruited and randomized into 5 groups for 90 days. Group one added one normal egg to their daily diet and group two received a lutein enriched egg-yolk based beverage. Group three added one lutein enriched egg and group four one zeaxanthin enriched egg to their diet. Group five was the control group and individuals in this group did not modify their daily diet. Serum lutein and zeaxanthin concentrations and macular pigment densities were obtained at baseline, day 45 and day 90. Macular pigment density was measured by heterochromatic flicker photometry. Serum lutein concentration in the lutein enriched egg and egg yolk-based beverage groups increased significantly ($p<0.001$, 76% and 77%). A strong increase in the serum zeaxanthin concentration was observed in individuals receiving zeaxanthin enriched eggs ($P< 0.001$, 430%). No changes were observed in macular pigment density in the various groups tested. The results indicate that daily consumption of lutein or zeaxanthin enriched egg yolks as well as an egg yolk-based beverage show increases in serum lutein and zeaxanthin levels that are comparable with a daily use of 5 mg supplements.

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Adv Exp Med Biol. 2014;801:783-9. doi: 10.1007/978-1-4614-3209-8_98.

Antioxidant therapy for retinal disease.

Kiang AS, Humphries MM, Campbell M, Humphries P.

Abstract: Disease mechanisms associated with retinal disease are of immense complexity, mutations within 45 genes having been implicated, for example, in retinitis pigmentosa, while interplay between genetic, environmental, and demographic factors can lead to diabetic retinopathy, age-related macular

degeneration, and glaucoma. In light of such diversity, any therapeutic modality that can be targeted to an early molecular process instrumental in multiple forms of disease, such as oxidative stress, holds much attraction. Here, we provide a brief overview of a selection of compounds displaying antioxidant activity, which have been shown to slow down degeneration of retinal tissues and highlight suggested modes of action.

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J Ophthalmol. 2014;2014:901686. Epub 2014 Jan 23.

Do Nutritional Supplements Have a Role in Age Macular Degeneration Prevention?

Pinazo-Durán MD, Gómez-Ulla F, Arias L, Araiz J, Casaroli-Marano R, Gallego-Pinazo R, García-Medina JJ, López-Gálvez MI, Manzanas L, Salas A, Zapata M, Diaz-Llopis M, García-Layana A.

Purpose: To review the proposed pathogenic mechanisms of age macular degeneration (AMD), as well as the role of antioxidants (AOX) and omega-3 fatty acids (ω -3) supplements in AMD prevention.

Materials and Methods: Current knowledge on the cellular/molecular mechanisms of AMD and the epidemiologic/experimental studies on the effects of AOX and ω -3 were addressed all together with the scientific evidence and the personal opinion of professionals involved in the Retina Group of the OFTARED (Spain).

Results: High dietary intakes of ω -3 and macular pigments lutein/zeaxanthin are associated with lower risk of prevalence and incidence in AMD. The Age-Related Eye Disease study (AREDS) showed a beneficial effect of high doses of vitamins C, E, beta-carotene, and zinc/copper in reducing the rate of progression to advanced AMD in patients with intermediate AMD or with one-sided late AMD. The AREDS-2 study has shown that lutein and zeaxanthin may substitute beta-carotene because of its potential relationship with increased lung cancer incidence.

Conclusion: Research has proved that elder people with poor diets, especially with low AOX and ω -3 micronutrients intake and subsequently having low plasmatic levels, are more prone to developing AMD. Micronutrient supplementation enhances antioxidant defense and healthy eyes and might prevent/retard/ modify AMD.

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Adv Exp Med Biol. 2014;801:301-7. doi: 10.1007/978-1-4614-3209-8_38.

A mechanistic review of cigarette smoke and age-related macular degeneration.

Woodell A, Rohrer B.

Abstract: Age-related macular degeneration (AMD), a complex disease stemming from both genetic abnormalities and environmental insults, is the most common form of visual impairment in elderly individuals of the Western world. Many potential etiologies are linked to AMD, but smoking is the leading environmental insult associated with this maculopathy. Smoke-induced damage is mediated in part through direct oxidation, depletion of antioxidants, complement activation, and vascular transmutations. Clinically, these mechanisms manifest themselves as keystones of atrophic AMD: retinal pigment epithelium degeneration, formation of extracellular deposits such as drusen, and thickening of Bruch's membrane. Furthermore, smoking induces angiogenesis and choroidal neovascularization, advancing the course of the disease to late-stage AMD. Further exploration of the biological processes affected by cigarette smoke exposure will provide greater insight into the pathogenesis of AMD.

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Surv Ophthalmol. 2014 Jan 27. pii: S0039-6257(14)00023-X. doi: 10.1016/j.survophthal.2014.01.001. [Epub ahead of print]

The role of omega-3 and micronutrients in age-related macular degeneration.

Querques G, Souied EH.

Abstract: Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss in the United States, Europe, and other developed countries. Although the pathogenesis of AMD remains unclear, current evidence suggests a multifactorial aetiology. Nutrition may play an important role in the development and progression of AMD. There have been several epidemiological studies suggesting that omega-3 fatty acids could have a protective role in AMD, but a beneficial effect remains to be demonstrated in randomized controlled trials. There also exists a substantial body of evidence suggesting that protection against AMD may be provided by specific micronutrients (vitamins and minerals and antioxidants). The identification of risk factors for the development and progression of AMD is of particular importance for understanding the origins of the disorder and for establishing strategies for its prevention. We examine the relationship between dietary omega-3 intake and the incidence and progression of AMD, as well as the role of omega-3 supplementation in the prevention of the disorder, and also explore the role of other micronutrients in AMD.

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