

Issue 321

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This free weekly bulletin lists the latest published research articles on macular degeneration (MD) and some other macular diseases as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases.

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Drug treatment

J Ophthalmol. 2017;2017:7432739. Epub 2017 Feb 20.

Comparison of Progression Rate of Retinal Pigment Epithelium Loss in Patients with Neovascular Age-Related Macular Degeneration Treated with Ranibizumab and Aflibercept.

Wons J, Wirth MA, Graf N, Becker MD, Michels S.

Purpose: Retinal pigment epithelium (RPE) loss in neovascular age-related macular degeneration (nAMD) seem to have a linear progression but might be influenced by the treatment. The purpose of the study is the comparison of RPE loss over three years in patients treated with intravitreal ranibizumab to patients who were switched to aflibercept.

Methods: A retrospective analysis with 96 eyes switched to aflibercept was conducted. The progression rate of RPE loss was evaluated in patients who showed atrophy one year prior to switch ($n = 17$) or on switch date ($n = 19$). The RPE loss was evaluated by spectral domain optical coherence tomography (SD-OCT). Further, 22 eyes from patients treated with ranibizumab were compared.

Results: The median yearly progression of RPE loss after square root transformation showed no significant difference in the year prior to switch compared to the year after switch ($p = 0.854$). In patients who received only ranibizumab, the median yearly progression of RPE loss was 0.15 mm/y, for aflibercept patients, 0.13 mm/y. This difference was not statistically significant ($p = 0.172$).

Conclusions: There seems to be a linear progression rate of RPE loss in patients treated with ranibizumab as well as in patients with aflibercept. No significant increase of progression rate was found after switch to aflibercept.

PMID: 28316836 PMCID: PMC5338067

J Fr Ophtalmol. 2017 Mar 21. [Epub ahead of print]

[Real life visual and anatomic outcomes of aflibercept treatment for treatment-naïve patients with exudative age-related macular degeneration]. [Article in French]

Duval MV, Rougier MB, Delyfer MN, Combillet F, Korobelnik JF.

Abstract: Anti-VEGF therapies have revolutionized the treatment of neovascular age-related macular degeneration (AMD).

PURPOSE: The goal of this study was to evaluate the "real life" visual and anatomical outcomes of aflibercept treatment for treatment-naïve patients with exudative AMD.

METHODS: This was a retrospective study of patients treated with aflibercept in the department of Ophthalmology at the University Hospital of Bordeaux between November 2013 and July 2015. The follow-up period varied from 3months to 2years. All patients received an induction phase with 3monthly intravitreal injections (IVT) followed by personalized monitoring. ETDRS best-corrected visual acuity (BCVA), fundus examination and OCT were performed at each visit. Data were collected at day 0, 3 months, 6, 9, 12months, 18 and 24months.

RESULTS: Forty-three eyes of forty patients, mean age 77.7years, were included, with a minimum of 3months follow-up. Twenty-five eyes were followed for 1year; 5 eyes for two years. At baseline, the mean BCVA was 55.7 letters. Patients received 7.5 injections on average the first year and 2.6 the 2nd year. The mean gain of visual acuity was +7.3 letters at 3 months, +6.2 letters at 12 months, and +6.8 letters at 2years. Anatomically, the OCT data showed a decline of all parameters. The central macular thickness decreased by 118.3µm at 3months, 136.4µm at 12months and 65.5µm at 2years.

CONCLUSION: Aflibercept can achieve effective visual and anatomical outcomes with results, which approach the pivotal studies, despite the use of personalized protocols and longer monitoring intervals.

PMID: 28341388

J Cell Mol Med. 2017 Mar 22. [Epub ahead of print]

A novel bispecific molecule delivered by recombinant AAV2 suppresses ocular inflammation and choroidal neovascularization.

Li Y, Zhu P, Verma A, Prasad T, Deng H, Yu D, Li Q.

Abstract: Elevated vascular endothelial growth factor (VEGF) and complement activation are implicated in the pathogenesis of different ocular diseases. The objective of this study was to investigate the hypothesis that dual inhibition of both VEGF and complement activation would confer better protection against ocular inflammation and neovascularization. In this study, we engineered a secreted chimeric VEGF inhibitor domain (VID), a complement inhibitor domain (CID) and a dual inhibitor (ACVP1). Vectors expressing these three inhibitors were constructed and packaged into AAV2 (sextY-F) particles. The expression and secretion of the proteins were validated by Western blot. The effects of these inhibitors expressed from AAV2 vectors were examined in endotoxin-induced uveitis (EIU), experimental autoimmune uveoretinitis (EAU) and choroidal neovascularization (CNV) mouse models. The AAV2 vectors expressing the CID- and ACVP1-attenuated inflammation in EIU and EAU model, whereas the vector expressing VID showed improved retinal structure damaged by EAU, but not affect the infiltration of inflammatory cells in EAU or EIU eyes. Both VID and CID vectors improved laser-induced retinal and choroid/RPE injuries and CNV, whereas ACVP1 vector provided significantly better protection. Our results suggest that gene therapy targeting VEGF and complement components could provide an innovative and long-term strategy for ocular inflammatory and neovascular diseases.

PMID: 28332318

PLoS One. 2017 Mar 27;12(3):e0174340. eCollection 2017.

Aqueous cytokine levels are associated with reduced macular thickness after intravitreal ranibizumab for diabetic macular edema.

Shiraya T, Kato S, Araki F, Ueta T, Miyaji T, Yamaguchi T.

PURPOSE: It is controversial whether the administration of anti-vascular endothelial growth factor drugs for diabetic macular edema (DME) affects intraocular inflammatory cytokines. In this study, we measured cytokine concentration in aqueous humor before and after intravitreal injection of ranibizumab (IVR). The

aim was to determine changes in cytokine concentration and their effects on DME reduction.

METHODS: Twelve patients (13 eyes) with DME received two IVR (0.5 mg) with a 1 month interval, and a total of 26 aqueous humor samples were obtained. Macular thickness was measured with an optical coherence tomography (OCT) using thickness-map mode with an Early Treatment Diabetic Retinopathy Study (ETDRS) 9-zone grid that was divided into two zones: a central circle with a diameter of 1 mm (zone1); and an outer circle with a diameter of 6 mm (zone2).

RESULTS: The concentration of eotaxin-1 in aqueous humor samples decreased significantly after IVR. Baseline cytokine concentration was associated with IVR-induced DME reduction. In zone1, higher baseline concentration of interferon-induced protein (IP)-10, and in zone 2, higher baseline concentration of granulocyte-macrophage colony-stimulating factor, IP-10, and tumor necrosis factor (TNF) α ; and lower baseline concentration of eotaxin-1, interleukin (IL)-5, and IL-8 were associated with improved DME. Cytokine changes were associated with IVR-induced DME reduction. In zone1, lower concentration of IP-10 compared to baseline or higher concentration of macrophage inflammatory protein (MIP) - α , and in zone 2, lower concentration of IL-5 compared to baseline, IL-8, and IP-10 or higher concentration of eotaxin-1 and MIP-1 β were associated with improved DME.

CONCLUSIONS: These findings suggest that ranibizumab affects the concentration of cytokines in aqueous humor. Various cytokines contribute to a decrease in retinal thickness, both in the center of the macula and in a larger area of the retina.

PMID: 28346545

Retina. 2017 Jan 23. [Epub ahead of print]

LONG-TIME OUTCOME IN PATIENTS TREATED WITH RANIBIZUMAB FOR DIABETIC MACULAR EDEMA: A 4-Year Study.

Epstein D, Amrén U.

PURPOSE: To investigate the long-time visual outcome in patients with diabetic macular edema treated with ranibizumab in an ordinary clinical setting.

METHODS: One hundred two eyes of 80 patients were followed for 4 years. All patients received a loading dose of 3 monthly ranibizumab 0.5-mg injections. From Month 3 to Month 48, patients received ranibizumab reinjections pro re nata based on disease activity.

RESULTS: Excluding deaths, the 4-year visit was completed by 82% of the study eyes. The best-corrected visual acuity improved by 6.6 Early Treatment Diabetic Retinopathy Study letters at 4 years ($P < 0.001$). The patients received a mean of 7.7 ± 3.4 ranibizumab injections for 4 years. The number of injections (mean $\pm$ SD) given were 4.7 (1.1), 1.4 (1.4), 0.7 (1.1), and 0.9 (1.4) during Years 1 to 4, respectively. No difference in the injections needed was seen between patients who had previously received focal/grid laser and treatment-naïve subjects.

CONCLUSION: The gain in the best-corrected visual acuity achieved after the initial loading dose was sustained over time with a pro re nata regimen. The number of injections needed to maintain the best-corrected visual acuity was low during the study period.

PMID: 28323678

Ophthalmic Res. 2017 Mar 24. [Epub ahead of print]

Intravitreal Dexamethasone Implant versus Intravitreal Ranibizumab for the Treatment of Macular Edema Secondary to Retinal Vein Occlusion in a Chinese Population.

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Gu X, Yu X, Song S, Dai H.

BACKGROUND: The aim of this work was to compare the efficacy of intravitreal dexamethasone implant (Ozurdex) and intravitreal ranibizumab (Lucentis) in the treatment of macular edema (ME) caused by retinal vein occlusion (RVO).

METHODS: Thirty-two ME cases treated with Ozurdex and 32 ME cases treated with ranibizumab were enrolled, with 26 central (C)RVO and 6 branch (B)RVO subjects in each group. We compared the results of best-corrected visual acuity (BCVA), central retinal thickness, number of injections, and intraocular pressure (IOP) at 1, 2, 3, and 6 months after injection.

RESULTS: BCVA in both groups at each follow-up were significantly increased compared to baseline with no statistical difference between the groups. Ozurdex and ranibizumab successfully reduced CMT at each follow-up. Both CRVO and BRVO patients had significant between-group differences in the mean number of injections. Among the CRVO patients, IOP in the Ozurdex group was significantly increased compared to baseline and the ranibizumab group at 1, 2, and 3 months postinjection.

CONCLUSIONS: Intravitreal injection of Ozurdex and ranibizumab can effectively control ME secondary to RVO and increase a patient's BCVA. The advantages of Ozurdex are fewer injections and longer efficacy, while the advantages of ranibizumab include fewer side effects.

PMID: 28334720

Eur J Ophthalmol. 2017 Feb 28:0. [Epub ahead of print]

Real-world outcomes of anti-VEGF treatment for retinal vein occlusion in Portugal.

Vaz-Pereira S, Marques IP, Matias J, Mira F, Ribeiro L, Flores R.

PURPOSE: Retinal vein occlusion (RVO) is an important cause of visual disability in the modern world. We aim to evaluate the real-world outcomes of patients with RVO treated with anti-vascular endothelial growth factor (VEGF) in Portugal.

METHODS: We performed a retrospective, observational, multicenter study including 8 centers across Portugal and 200 patients treated with either ranibizumab or bevacizumab. Data were collected at 3 time points: time of diagnosis (0 time point) and 6 and 12 months after initiating treatment. Demographic and clinical data were collected.

RESULTS: Median visual acuity (VA) and central macular thickness (CMT) improved in the branch RVO (BRVO), central RVO (CRVO), bevacizumab, and ranibizumab groups at 6 and 12 months compared to baseline, with CMT improving further only in the CRVO and ranibizumab groups between 6 and 12 months ($p = 0.002$ and $p = 0.001$, respectively). The CMT was lower in the ranibizumab group compared to the bevacizumab group both at 6 and 12 months ($p < 0.02$). Median CMT improved in both the good and poor baseline VA groups at 6 and 12 months compared to baseline ($p < 0.001$). Median VA only improved for the group with poor baseline VA at 6 and 12 months of follow-up ($p < 0.001$). Regression analysis identified several baseline variables as predictors of visual outcomes at 6 and 12 months, with different results depending on the analyzed group.

CONCLUSIONS: Both treatments were effective, although less effective than results reported in clinical trials. The morphologic response was better with ranibizumab compared to bevacizumab, although functionally there were no differences.

PMID: 28315518

Ophthalmol Ther. 2017 Mar 21. [Epub ahead of print]

A Review of Ranibizumab for the Treatment of Diabetic Retinopathy.

Stewart MW.

INTRODUCTION: Laser photocoagulation has been the standard treatment for diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR) for several decades. The discovery of vascular endothelial growth factor (VEGF) and the subsequent determination of its critical role in the development DME and PDR has led to the development of VEGF inhibitory drugs. Ranibizumab was the first anti-VEGF drug approved for the treatment of both DME and diabetic retinopathy in eyes with DME.

METHODS: Medline searches with the keywords "ranibizumab," "diabetic macular edema," and "proliferative diabetic retinopathy" were performed to identify pertinent pre-clinical studies and clinical trials. Top-line data, with emphasis on pivotal trials, was identified and incorporated into this manuscript. Findings from small uncontrolled trials were generally not used unless they filled important gaps in our understanding of anti-VEGF therapy.

RESULTS: Ranibizumab is a recombinant humanized antibody fragment that binds all isoforms of VEGF-A with high affinity. Three parallel lines of clinical research have produced level I evidence supporting the superiority of ranibizumab over laser photocoagulation for the treatment of DME. Regular injections also lead to improvement in diabetic retinopathy severity scores in a large minority of eyes. Ranibizumab is effective for PDR and produces less visual field loss than laser photocoagulation. It has an excellent safety profile, with low incidence of ocular and systemic adverse events.

CONCLUSIONS: Ranibizumab has become a frequently used first-line therapy for the treatment of DME. Emerging data suggest that it may become an important treatment for DR and PDR.

PMID: 28324452

Medicine (Baltimore). 2017 Mar;96(12):e6422.

Effect of topical isopropyl unoprostone on macular atrophy progression in eyes with exudative age-related macular degeneration.

Shiragami C, Miyake M, Fujiwara A, Morizane Y, Tsujikawa A, Yamashita A, Shiraga F.

BACKGROUND: To evaluate the efficacy and safety of topical isopropyl unoprostone (IU) in treating macular atrophy in age-related macular degeneration (AMD) patients.

METHODS: Fifty-two AMD patients with macular atrophy were included and randomly assigned (1:1) to the treatment (topical 0.15% IU) or placebo group. Subjects used study eye drops 3 times a day for 54 weeks. The macular atrophy was documented on fundus autofluorescence photographs and measured using RegionFinder. The enlargement rate of macular atrophy and the changes in visual acuity were examined statistically between baseline and 54 weeks.

RESULTS: Forty-eight subjects were included in the analyses because 4 subjects withdrew from the study. The differences between the IU and placebo groups in mean and median area of macular atrophy were not statistically significant at baseline. The baseline median lesion size of macular atrophy was 2.33mm in the IU group and 1.63mm in the placebo group ($P=0.51$). The intergroup difference in the enlargement ratio of macular atrophy ($21\pm15\%$ in the IU group and $111\pm96\%$ in the placebo group) was statistically significant ($P<0.001$). Additionally, visual acuity tended to improve over baseline in the IU group. No serious adverse events were observed.

CONCLUSIONS: Topical IU therapy is safe and effective for treating macular atrophy in AMD patients.

PMID: 28328847

J Fr Ophtalmol. 2017 Mar 16. [Epub ahead of print]

[Individualized management of patients with exudative AMD, IOI protocol: Injection-observational-individualization]. [Article in French]

Semoun O, Cohen SY, Srour M, Creuzot-Garchet C, Oubraham-Mebroukine H, Kodjikian L, Devin F, Souied EH; Comité scientifique de la Fédération France Macula.

Abstract: Wet macular degeneration remains a major cause of visual impairment in people over 55years. Through a group of experts belonging to the Federation France Macula, we review the treatment of wet AMD and provide recommendation with a 3 phases protocol called IOI.

PMID: 28318717

J Fr Ophtalmol. 2017 Mar 17. [Epub ahead of print]

[Ranibizumab tachyphylaxis in a case of macular edema related to central retinal vein occlusion: Lasting effectiveness of switching to aflibercept]. [Article in French]

Gambrelle J, Robinet A.

PMID: 28318715

J Fr Ophtalmol. 2017 Mar 20. [Epub ahead of print]

[Response to aflibercept in patients with fibrovascular pigment epithelial detachment refractory to ranibizumab in exudative age-related macular degeneration]. [Article in French]

Tran TH, Dumas S, Coscas F.

PMID: 28336285

Ophthalmology. 2017 Apr;124(4):e37-e38.

Re: Wells et al.: Aflibercept, Bevacizumab, or Ranibizumab for diabetic macular edema: two year results from a comparative effectiveness randomized clinical trial (Ophthalmology. 2016;123:1351-1359).

Venkatesh P.

PMID: 28335948

Other treatment & diagnosis

Retina. 2017 Mar 23. [Epub ahead of print]

ADULT-ONSET FOVEOMACULAR VITELLIFORM DYSTROPHY EVALUATED BY MEANS OF OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY: A Comparison With Dry Age-Related Macular Degeneration and Healthy Eyes.

Toto L, Borrelli E, Mastropasqua R, Di Antonio L, Mattei PA, Carpineto P, Mastropasqua L.

PURPOSE: To investigate alterations of superficial and deep retinal vascular densities, as well as of

choroidal thickness, in patients affected by adult-onset foveomacular vitelliform dystrophy (AOFVD).

METHODS: A total of 22 eyes (15 patients) affected by AOFVD were recruited in the study. Furthermore, 20 eyes of 20 healthy subjects and 20 eyes of 18 patients affected by intermediate dry age-related macular degeneration (AMD) were enrolled. All patients underwent a complete ophthalmologic examination, including optical coherence tomography angiography. Outcome measures were superficial vessel density, deep vessel density, and choroidal thickness.

RESULTS: Parafoveal superficial vessel density was increased in patients with AOFVD compared with the AMD group ($50.6 \pm 4.3\%$ and $46.3 \pm 4.3\%$, respectively, $P = 0.016$). Parafoveal deep vessel density was $57.9 \pm 6.4\%$ in patients with AOFVD, $52.2 \pm 3.8\%$ in patients with AMD, and $52.7 \pm 6.0\%$ in healthy controls ($P = 0.006$ and $P = 0.035$, respectively, after comparison with the AOFVD group).

CONCLUSION: We demonstrated that both superficial and deep vessel densities were significantly increased in patients with AOFVD, after the comparison with intermediate patients with AMD. These findings suggest that the pathogenic mechanisms in AOFVD are different from those in AMD and that optical coherence tomography angiography could be useful in differentiate early stages of these two diseases.

PMID: 28338556

Surv Ophthalmol. 2017 Mar 20. [Epub ahead of print]

Retinal Pigment Epithelium Tears: Classification, Pathogenesis, Predictors, and Management.

Ersoz MG, Karacorlu M, Arf S, Sayman Muslubas I, Hocaoglu M.

Abstract: Various eye conditions cause tears in the retinal pigment epithelium (RPE). The most common cause of an RPE tear is vascularized retinal pigment epithelial detachment (PED) in patients with exudative age-related macular degeneration. Although RPE tears can develop spontaneously in vascularized PEDs, most recent cases have been associated with anti-vascular endothelial growth factor (VEGF) injections. The subretinal fluid within the PED applies hydrostatic pressure to the RPE and stretches it. The PED enlarges as the hydrostatic pressure increases. Contraction of the choroidal neovascular membrane (CNVM) adds tractional forces to the RPE monolayer. Especially in larger PEDs, the risk of an RPE tear increases after anti-VEGF therapy owing to increasing contraction of the CNVM. The risk factors and predictors defined by retinal imaging can contribute to prevention of RPE tears, and modified therapies can be used for patients at most risk; however, there is no proven method for prevention of RPE tear. After tear formation, in the presence of an active CNVM, anti-VEGF injections should be repeated until the underlying disease has been suppressed. When the subretinal fluid is present for more than 6 months, the denuded area is covered with thickened fibrotic tissue. We reviewed the literature to describe the classification, epidemiology, mechanisms of development and repair of RPE tears, diagnosis, risk factors and predictors, prevention, and management.

PMID: 28336128

Transl Vis Sci Technol. 2017 Mar 13;6(2):3. eCollection 2017.

Automated Brightness and Contrast Adjustment of Color Fundus Photographs for the Grading of Age-Related Macular Degeneration.

Tsikata E, Laíns I, Gil J, Marques M, Brown K, Mesquita T, Melo P, da Luz Cachulo M, Kim IK, Vavvas D, Murta JN, Miller JB, Silva R, Miller JW, Chen TC, Husain D.

PURPOSE: The purpose of this study was to develop an algorithm to automatically standardize the

brightness, contrast, and color balance of digital color fundus photographs used to grade AMD and to validate this algorithm by determining the effects of the standardization on image quality and disease grading.

METHODS: Seven-field color photographs of patients (>50 years) with any stage of AMD and a control group were acquired at two study sites, with either the Topcon TRC-50DX or Zeiss FF-450 Plus cameras. Field 2 photographs were analyzed. Pixel brightness values in the red, green, and blue (RGB) color channels were adjusted in custom-built software to make the mean brightness and contrast of the images equal to optimal values determined by the Age-Related Eye Disease Study (AREDS) 2 group.

RESULTS: Color photographs of 370 eyes were analyzed. We found a wide range of brightness and contrast values in the images at baseline, even for those taken with the same camera. After processing, image brightness variability (brightest image-dimmest image in a color channel) was reduced 69-fold, 62-fold, and 96-fold for the RGB channels. Contrast variability was reduced 6-fold, 8-fold, and 13-fold, respectively, after adjustment. Of the 23% images considered nongradable before adjustment, only 5.7% remained nongradable.

CONCLUSIONS: This automated software enables rapid and accurate standardization of color photographs for AMD grading.

TRANSLATIONAL RELEVANCE:

This work offers the potential to be the future of assessing and grading AMD from photos for clinical research and teleimaging.

PMID: 28316876 PMCID: PMC5354475

Cell Physiol Biochem. 2017 Mar 16;41(4):1413-1423. [Epub ahead of print]

Circulating miRNAs as Potential Biomarkers of Age-Related Macular Degeneration.

Ren C, Liu Q, Wei Q, Cai W, He M, Du Y, Xu D, Wu Y, Yu J.

Background: Age-related macular degeneration (AMD) is one of the leading causes of irreversible blindness of the elder people. This research was intended to demonstrate the different expression of microRNAs (miRNA) in AMD patients and whether they can be used as biomarkers for AMD.

METHODS: MiRNAs expression was measured by microarray of 6 AMD cases and 6 gender matched controls. In a larger-sample case-control study with 126 AMD cases and 140 controls, whole blood samples were detected for the differences of miRNA expression.

RESULTS: A total of 216 differentially expressed miRNAs (111 increased and 105 decreased miRNAs) were detected from circulating miRNA microarray. Expanded case-control study results showed that the expression of miR-27a-3p, miR-29b-3p and miR-195-5p was increased significantly. Moreover, the level of miR-27a is higher in patients with wet AMD compared to patients with dry AMD. All 3 miRNAs showed a potential diagnostic value for AMD.

CONCLUSION: Circulating miRNA levels were significantly varied in AMD patients. Three miRNAs, miR-27a-3p, miR-29b-3p and the miR-195-5p, might be potential diagnostic biomarkers for AMD.

PMID: 28315863

Retina. 2017 Apr;37(4):680-686.

DOME-SHAPED MACULA IN MYOPIC EYES: Twelve-Month Follow-up.

Lorenzo D, Arias L, Choudhry N, Millan E, Flores I, Rubio MJ, Cobos E, García-Bru P, Filloy A, Caminal JM.

PURPOSE: To study the long-term clinical course of dome-shaped macula in myopic eyes and to evaluate treatment efficacy for subretinal fluid (SRF) as a related complication.

METHODS: A retrospective, single-center consecutive case series study was conducted. The authors analyzed myopic eyes with dome-shaped macula in patients who presented for evaluation of decreased vision. Dome-shaped macula was defined as a convexity of the retina-choroidal macular complex seen on spectral domain optical coherence tomography images. All patients were followed for at least 12 months (mean, 25 months). Fluorescein angiography and/or indocyanine green angiography were performed in cases with SRF to rule out choroidal neovascularization.

RESULTS: A total of 56 dome-shaped macula eyes from 36 patients were included in the study (bilateral in 55% of patients). Mean patient age was 56.9 ± 13.1 years. The mean spherical equivalent was -9.1 ± 6.0 diopters; 53% of eyes were considered highly myopic (>-6 diopters) and 47% of eyes were mildly myopic. In most cases (37 eyes; 66.1%), the dome-shaped macula was detected on vertical spectral domain optical coherence tomography scan patterns. No significant changes ($P \geq 0.1$) were observed in mean best-corrected visual acuity or mean central foveal thickness from baseline to final follow-up. Subretinal fluid was present in 29 eyes (51.8%) at baseline, with no differences in best-corrected visual acuity in eyes with and without SRF ($P \geq 0.05$). Nineteen of the 29 SRF eyes were treated: 8 underwent low-fluence photodynamic therapy, whereas 7 received bevacizumab, and 4 ranibizumab. No significant differences were found between treated and untreated SRF eyes in best-corrected visual acuity improvement ($P \geq 0.1$), or complete resolution of SRF ($P \geq 0.1$). Likewise, photodynamic therapy did not yield any significant benefit versus untreated eyes in best-corrected visual acuity or improvement of SRF.

CONCLUSION: Dome-shaped macula is a condition associated with myopic eyes that seems to remain stable over time in terms of vision and macular profiles. It is often associated with chronic SRF, for which no effective treatment is current available. However, SRF does not seem to be a significant cause of visual impairment.

PMID: 28333783

Semin Ophthalmol. 2017 Mar 22;1-9. [Epub ahead of print]

The Role of mf-ERG in the Diagnosis and Treatment of Age-Related Macular Degeneration: Electrophysiological Features of AMD.

Moschos MM, Nitoda E.

INTRODUCTION: Age-related macular degeneration (AMD) is the leading cause of visual dysfunction worldwide, affecting 9-25% of individuals between 65 and 75 years old.

METHODS: We have reviewed the published articles investigating the role of multifocal electroretinogram (mf-ERG) in the diagnosis and treatment of AMD.

RESULTS: Visual evoked potentials have revealed decreased amplitudes and higher latencies in patients with AMD, while the degeneration of photoreceptors and abnormalities of retinal pigment epithelium can be identified by electro-oculogram recordings. Moreover, ERG can detect the functional abnormalities observed in AMD and evaluate each therapeutic approach. The record of local electrophysiological responses coming from different retinal areas can be accurately performed by mfERG.

CONCLUSION: The accuracy of mfERG in detecting the degeneration of photoreceptors, as well the disturbances of macular function, could be useful both in the early diagnosis of AMD and the assessment of treatment efficacy.

PMID: 28328288

Pathogenesis

Invest Ophthalmol Vis Sci. 2017 Mar 1;58(3):1801-1810.

Protective Effect of Met12, a Small Peptide Inhibitor of Fas, on the Retinal Pigment Epithelium and Photoreceptor After Sodium Iodate Injury.

Xiao J, Yao J, Jia L, Lin C, Zacks DN.

PURPOSE: A major problem in macular degeneration is the inability to reduce RPE and photoreceptor death. These cells die by necroptosis and apoptosis, respectively, but the upstream activator(s) of these death pathways is unknown. In this study, we use the sodium iodate (NaIO₃) model of oxidative stress to test the hypothesis that activation of the Fas receptor contributes to the death of the RPE and photoreceptors.

METHODS: Sodium iodate was injected in Brown-Norway rats via femoral vein injection. Both in vivo (fundus photography, optical coherence tomography, and fluorescein angiography) and ex vivo (histology, immunohistochemistry, Western blot, and RT-PCR) analyses of the RPE and retina were conducted at baseline, as well as at various times post NaIO₃ injection. The ability of intravitreal injection of Met12, a small peptide inhibitor of the Fas receptor, to prevent RPE and photoreceptor cell death was assessed.

RESULTS: Injection of NaIO₃ led to Fas-mediated activation of both necroptosis and apoptosis in the RPE and photoreceptors, respectively. This was accompanied by a significant increase in the number of microglia/macrophages in the outer retina. Met12 significantly reduced the activation of the Fas-mediated death pathways, resulting in reduced RPE and photoreceptor death and a decreased immune response.

CONCLUSIONS: Our results demonstrate that NaIO₃ activates Fas-mediated cell death, both in the RPE and photoreceptor, and that a small peptide antagonist of the Fas receptor, Met12, significantly reduces the extent of this cell death. These findings suggest a role for Fas inhibition to protect the RPE and photoreceptors from death due to oxidative stress.

PMID: 28346613

Sci Rep. 2017 Mar 27;7:45081.

Elevated angiopoietin 2 in aqueous of patients with neovascular age related macular degeneration correlates with disease severity at presentation.

Ng DS, Yip YW, Bakthavatsalam M, Chen LJ, Ng TK, Lai TY, Pang CP, Brelén ME.

Abstract: Angiopoietin 2 (ANG2) is a proangiogenic cytokine which may have an implication in neovascular age related macular degeneration (nAMD). In 24 eyes of 24 subjects presenting with treatment naïve nAMD and 26 eyes of 26 control patients, aqueous humor samples were collected at the time of intervention (intravitreal injection of anti-vascular endothelial growth factor or cataract extraction). Best corrected visual acuity (BCVA) with and central macular thickness (CMT) using optical coherence tomography (OCT) were measured before each injection in the nAMD group. Aqueous cytokine levels were determined by immunoassay using a multiplex array (Quansys Biosciences, Logan, UT). Levels of ANG2 in the aqueous were significantly higher in nAMD patients than those of the control group ($p < 0.0001$), so were hepatocyte growth factor (HGF), interleukin-8 (IL-8) and tissue inhibitor of metalloproteinase 1 (TIMP 1), all with $p < 0.001$. ANG2 correlated with worse BCVA ($r = 0.44$, p -value = 0.027) and greater CMT ($r = 0.66$, p -value < 0.0001) on optical coherence tomography (OCT). ANG2 is upregulated in patients with nAMD and correlates with severity of disease at presentation.

PMID: 28345626

J Neurochem. 2017 Mar 27. [Epub ahead of print]

RS9, a novel Nrf2 activator, attenuates light-induced death of cells of photoreceptor cells and Müller glia cells.

Inoue Y, Shimazawa M, Noda Y, Nagano R, Otsuka T, Kuse Y, Nakano Y, Tsuruma K, Nakagami Y, Hara H.

Abstract: The retina is highly sensitive to oxidative stress because of its high consumption of oxygen associated with the phototransductional processes. Recent findings have suggested that oxidative stress is involved in the pathology of age-related macular degeneration (AMD), a progressive degeneration of the central retina. A well-known environmental risk factor is light exposure, as excessive and continuous light exposure can damage photoreceptors. Nuclear factor-erythroid 2-related factor 2 (Nrf2) is a transcriptional factor that controls antioxidative responses and phase 2 enzymes. Thus, we hypothesized that RS9, a specific activator of Nrf2, decreases light-induced retinal cell death in vivo and in vitro. Nrf2 was detected in the nucleus of the 661w cells exposed to RS9 and also after light exposure, and the Nrf2-antioxidant response element (ARE) binding was increased in 661w cells after exposure to RS9. Consequentially, the expression of the phase 2 enzyme's mRNAs of Ho-1, Nqo-1, and Gclm genes were increased in 661w cells after exposure to RS9. Further, RS9 decreased the light-induced death of 661W cells (2,500 lx, 24 h), and also reduced the functional damages and the histological degeneration of the nuclei in the outer nuclear layer (ONL) or the retina in the in vivo studies (8,000 lx, 3 h). HO-1 was increased after light exposure, and Nrf2 was translocated into the nucleus after light exposure in vivo. Silencing of Ho-1 reduced the protective effects of RS9 against light-induced death of 661w cells. These findings indicate that RS9 has therapeutic potential for retinal diseases that are aggravated by light exposure. This article is protected by copyright. All rights reserved.

PMID: 28345128

Brain Res. 2017 Mar 20. [Epub ahead of print]

Apigenin-7-diglucuronide protects retinas against bright light-induced photoreceptor degeneration through the inhibition of retinal oxidative stress and inflammation.

Bian M, Zhang Y, Du X, Xu J, Cui J, Gu J, Zhu W, Zhang T, Chen Y.

Abstract: Vision impairment in retinal degenerative diseases such as age-related macular degeneration is primarily associated with photoreceptor degeneration, in which oxidative stress and inflammatory responses are mechanistically involved as central players. Therapies with photoreceptor protective properties remain to be developed. Apigenin-7-diglucuronide (A7DG), a flavonoid glycoside, is present in an assortment of medicinal plants with anti-inflammatory or ant-oxidant activities. However, the pharmacological significance of A7DG remains unknown in vivo. The current study isolated A7DG from *Glechoma longituba* (Nakai) Kuprian and investigated the retinal protective effect A7DG in mice characterized by bright light-induced photoreceptor degeneration. The results showed that A7DG treatment led to remarkable photoreceptor protection in bright light-exposed BALB/c mice. Moreover, A7DG treatment alleviated photoreceptor apoptosis, mitigated oxidative stress, suppressed reactive gliosis and microglial activation and attenuated the expression of proinflammatory genes in bright light-exposed retinas. The results demonstrated for the first time remarkable photoreceptor protective activities of A7DG in vivo. Inhibition of bright light-induced retinal oxidative stress and retinal inflammatory responses was associated with the retinal protection conferred by A7DG. The work here warrants further evaluation of A7DG as a pharmacological candidate for the treatment of vision-threatening retinal degenerative disorders. Moreover, given the general implication of oxidative stress and inflammation in the pathogenesis of neurodegeneration, A7DG could be further tested for the treatment of other neurodegenerative disorders.

PMID: 28336272

J Ocul Pharmacol Ther. 2017 Mar 23. [Epub ahead of print]

New Insights on Complement Inhibitor CD59 in Mouse Laser-Induced Choroidal Neovascularization: Mislocalization After Injury and Targeted Delivery for Protein Replacement.

Schnabolk G, Beon MK, Tomlinson S, Rohrer B.

PURPOSE: The membrane attack complex (MAC) in choriocapillaris (CC) and retinal pigment epithelium (RPE) increase with age and disease (age-related macular degeneration). MAC assembly can be inhibited by CD59, a membrane-bound regulator. Here we further investigated the role of CD59 in murine choroidal neovascularization (CNV), a model involving both CC and RPE, and tested whether CR2-CD59, a soluble targeted form of CD59, provides protection.

METHODS: Laser-induced CNV was generated in wild type and CD59a-deficient mice (CD59^{-/-}). CNV size was measured by optical coherence tomography, and CR2-CD59 was injected intraperitoneally. Endogenous CD59 localization and MAC deposition were identified by immunohistochemistry and quantified by confocal microscopy. Cell-type-specific responses to MAC were examined in retinal pigment epithelial cells (ARPE-19) and microvascular endothelial cells (HMEC-1).

RESULTS: CD59 levels were severely reduced and protein was mislocalized in the RPE surrounding the lesion. CNV lesion size and subretinal fluid accumulation were exacerbated in CD59^{-/-} when compared with those in WT mice, and an increase in MAC deposition was noted. In contrast, CR2-CD59 significantly reduced both structural features of CNV severity. In vitro, MAC inhibition in ARPE-19 cells prevented barrier function loss and accelerated wound healing and cell adhesion, whereas in HMEC-1 cells, CR2-CD59 decelerated wound healing and cell adhesion.

CONCLUSION: These data further support the importance of CD59 in controlling ocular injury responses and indicate that pharmacological inhibition of the MAC with CR2-CD59 may be a viable therapeutic approach for reducing complement-mediated ocular pathology.

PMID: 28333572

Mol Vis. 2017 Mar 5;23:52-59. eCollection 2017.

The involvement of ATF4 and S-opsin in retinal photoreceptor cell damage induced by blue LED light.

Ooe E, Tsuruma K, Kuse Y, Kobayashi S, Shimazawa M, Hara H.

PURPOSE: Blue light is a high-energy emitting light with a short wavelength in the visible light spectrum. Blue light induces photoreceptor apoptosis and causes age-related macular degeneration or retinitis pigmentosa. In the present study, we investigated the roles of endoplasmic reticulum (ER) stress induced by blue light-emitting diode (LED) light exposure in murine photoreceptor cells.

METHODS: The murine photoreceptor cell line was incubated and exposed to blue LED light (464 nm blue LED light, 450 lx, 3 to 24 h). The expression of the factors involved in the unfolded protein response pathway was examined using quantitative real-time reverse transcription (RT)-PCR and immunoblot analysis. The aggregation of short-wavelength opsin (S-opsin) in the murine photoreceptor cells was observed with immunostaining. The effect of S-opsin knockdown on ATF4 expression in the murine photoreceptor cell line was also investigated.

RESULTS: Exposure to blue LED light increased the *bip*, *atf4*, and *grp94* mRNA levels, induced the expression of ATF4 protein, and increased the levels of ubiquitinated proteins. Exposure to blue LED light in combination with ER stress inducers (tunicamycin and dithiothreitol) induced the aggregation of S-opsin. S-opsin mRNA knockdown prevented the induction of ATF4 expression in response to exposure to blue LED light.

CONCLUSIONS: These findings indicate that the aggregation of S-opsin induced by exposure to blue LED light causes ER stress, and ATF4 activation in particular.

PMID: 28331281

Adv Exp Med Biol. 2017;964:285-297.

Peeking into Sigma-1 Receptor Functions Through the Retina.

Mavlyutov TA, Guo LW.

Abstract: This review discusses recent advances towards understanding the sigma-1 receptor (S1R) as an endogenous neuro-protective mechanism in the retina , a favorable experimental model system. The exquisite architecture of the mammalian retina features layered and intricately wired neurons supported by non-neuronal cells. Ganglion neurons, photoreceptors , as well as the retinal pigment epithelium, are susceptible to degeneration that leads to major retinal diseases such as glaucoma , diabetic retinopathy , and age-related macular degeneration (AMD), and ultimately, blindness. The S1R protein is found essentially in every retinal cell type, with high abundance in the ganglion cell layer. Ultrastructural studies of photoreceptors, bipolar cells, and ganglion cells show a predominant localization of S1R in the nuclear envelope. A protective role of S1R for ganglion and photoreceptor cells is supported by in vitro and in vivo experiments. Most recently, studies suggest that S1R may also protect retinal neurons via its activities in Müller glia and microglia. The S1R functions in the retina may be attributed to a reduction of excitotoxicity, oxidative stress , ER stress response, or inflammation. S1R knockout mice are being used to delineate the S1R-specific effects. In summary, while significant progress has been made towards the objective of establishing a S1R-targeted paradigm for retinal neuro-protection , critical questions remain. In particular, context-dependent effects and potential side effects of interventions targeting S1R need to be studied in more diverse and more clinically relevant animal models.

PMID: 28315278

Eur J Pharmacol. 2017 Mar 16. [Epub ahead of print]

Rimonabant, a selective cannabinoid1 receptor antagonist, protects against light-induced retinal degeneration in vitro and in vivo.

Imamura T, Tsuruma K, Inoue Y, Otsuka T, Ohno Y, Ogami S, Yamane S, Shimazawa M, Hara H.

Abstract: The endocannabinoid system is involved in some neurodegenerative diseases such as Alzheimer's disease. An endogenous constellation of proteins related to cannabinoid1 receptor signaling, including free fatty acids, diacylglycerol lipase, and N-acyl ethanolamine-hydrolyzing acid amidase, are localized in the murine retina. Moreover, the expression levels of endogenous agonists of cannabinoid receptors are changed in the vitreous fluid. However, the role of the endocannabinoid system in the retina, particularly in the light-induced photoreceptor degeneration, remains unknown. Therefore, we investigated involvement of the cannabinoid1 receptor in light-induced retinal degeneration using in vitro and in vivo models. To evaluate the effect of cannabinoid1 receptors in light irradiation-induced cell death, the mouse retinal cone-cell line (661W) was treated with a cannabinoid1 receptor antagonist, rimonabant. Time-dependent changes of expression and localization of retinal cannabinoid1 receptors were measured using Western blot and immunostaining. Retinal damage was induced in mice by exposure to light, followed by intravitreal injection of rimonabant. Electroretinograms and histologic analyses were performed. Rimonabant suppressed light-induced photoreceptor cell death. Cannabinoid1 receptor expression was upregulated by light exposure. Treatment with rimonabant improved both a- and b-wave amplitudes and the thickness of the outer nuclear layer. These results suggest that the cannabinoid1 receptor is involved in light-induced retinal degeneration and it may represent a therapeutic target in the light-induced

photoreceptor degeneration related diseases.

PMID: 28315677

Invest Ophthalmol Vis Sci. 2017 Mar 1;58(3):1726-1735.

MicroRNA Expression Patterns Involved in Amyloid Beta-Induced Retinal Degeneration.

Huang P, Sun J, Wang F, Luo X, Feng J, Gu Q, Liu T, Sun X.

PURPOSE: Dry age-related macular degeneration (AMD) is characterized by the accumulation of drusen under Bruch's membrane, and amyloid beta (A β) is speculated to be one of the key pathologic factors. While the detrimental effects of A β on retinas have been widely explored, A β -induced epigenetic regulatory changes have yet to be fully investigated. We therefore aimed to identify the microRNA (miRNA) expression profiles in an A β -induced mouse model of retinal degeneration.

METHODS: C57BL/6 mice were intravitreally injected with A β 1-40 or PBS and the eye tissues were collected for hematoxylin and eosin (H&E) staining, apoptosis immunofluorescence staining, and miRNA profiling. After filtering, 10 miRNAs and their target genes were chosen for quantitative RT-PCR (qRT-PCR) confirmations. Pathway analyses were employed for further bioinformatic analyses.

RESULTS: Hematoxylin and eosin-stained sections of retinal pigment epithelium (RPE)/neural retina tissue demonstrated degenerative alterations, and immunofluorescence testing revealed apoptosis within the retina after A β treatments. MicroRNA profiling revealed 61 miRNAs that were differentially expressed between the model and the control group. Among these, 38 miRNAs were upregulated (fold change > 1.5, $P < 0.05$) and 23 miRNAs were downregulated (fold change < 0.667, $P < 0.05$). Five of the 10 selected miRNAs (miR-142, miR-216, miR-155, miR-223, and miR-433) as well as several key target genes (CFH, IGF-1R, c-MET, and ABCA1) were confirmed by qRT-PCR analyses.

CONCLUSIONS: Our study is the first to profile the miRNA expression patterns and suggests that A β accumulation could lead to relevant biochemical alternations such as complement activation, barrier impairment, apoptosis, and positive feedback of A β production.

PMID: 28324113

Biomed Res Int. 2017;2017:3681707. Epub 2017 Feb 22.

PTEN Reduced UVB-Mediated Apoptosis in Retinal Pigment Epithelium Cells.

He J, Long C, Huang Z, Zhou X, Kuang X, Liu L, Liu H, Tang Y, Fan Y, Ning J, Ma X, Zhang Q, Shen H.

Abstract: Age-related macular degeneration (AMD) is a leading cause of blindness and progressive loss of central vision in the elderly population. The important factor of AMD pathogenesis is the degeneration of retinal pigment epithelial (RPE) cells by oxidative stress. Inactivation of PTEN can disrupt intercellular adhesion in the RPE cells, but the mechanism of oxidative stress is less known. Here we presented evidence that UVB-mediated oxidative stress induced apoptosis in ARPE-19 cells. Downregulation of the expression of PTEN in UVB-irradiative RPE cells triggered DNA damage and increased the level of UVB-induced apoptosis by activating p53-dependent pathway. However, overexpression of PTEN increased cell survival by suppressing p-H2A in response to DNA damage and apoptosis. When using Pifithrin- α (one of p53 inhibitors), the level of p53-dependent apoptosis was significantly lower than untreated, which suggested that p53 was possibly involved in PTEN-dependent apoptosis. Thus, it elucidated the molecular mechanisms of UVB-induced damage in RPE cells and may offer an alternative therapeutic target in dry AMD.

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Exp Eye Res. 2017 Mar 20. [Epub ahead of print]

Increased susceptibility to fundus camera-delivered light-induced retinal degeneration in mice deficient in oxidative stress response proteins.

Ding Y, Aredo B, Zhong X, Zhao CX, Ufret-Vincenty RL.

Abstract: Oxidative stress is an important contributor to the pathogenesis of many retinal diseases including age-related macular degeneration and retinal dystrophies. Light-induced retinal degeneration (LIRD) can serve as a model in which to study the response of the retina to stress. Of note, many genetic mutant mice are in a C57BL/6 J background and are thus resistant to the usual LIRD models. We recently developed a new model of fundus camera-delivered light-induced retinal degeneration (FCD-LIRD) which is effective in strains of mice expressing the light-resistant variant of RPE65 (450Met), including C57BL/6 J. In this work we investigated whether FCD-LIRD would be useful as a model in which to test the effect of genetic mutations on the response of the retina to stress. Furthermore, we tested whether oxidative stress plays an important role in the setting of this new FCD-LIRD model. FCD-LIRD was applied to C57BL/6 J mice and to mice simultaneously deficient in three proteins that are important in the response of the retina to oxidative stress (SOD1, DJ-1 and Parkin). Using fundus photography, we found that retinal damage was dramatically increased in the SOD1/DJ-1/Parkin deficient mice compared to C57BL/6 J. Outer retinal OCT volume and RPE cell morphology analysis in ZO-1-stained flat mounts added support to these findings. Gene expression analysis confirmed a strong oxidative stress response after FCD-LIRD, which was differentially altered in the SOD1/DJ1/Parkin deficient mice. We conclude that FCD-LIRD is useful to study the effect of genetic mutations on the response of the retina to light stress in light-resistant strains of mice. Furthermore, oxidative stress seems to be an important component of FCD-LIRD. Finally, we have established protocols to quantify the effect of FCD-LIRD on the retina and RPE which will be useful for future studies. Further dissection of the mechanisms by which the retina responds to light-induced oxidative stress may result in new strategies to modulate this response, which could lead to a reduction in retinal and RPE damage.

PMID: 28336262

Invest Ophthalmol Vis Sci. 2017 Mar 1;58(3):1764-1765.

Chronic, Systemic Interleukin-18 Does Not Promote Macular Degeneration or Choroidal Neovascularization.

Canna SW, Shi G, Gery I, Sen HN.

PMID: 28334374

Genetics

Mol Ther Nucleic Acids. 2017 Mar 17;6:302-314. Epub 2017 Feb 10.

Engineering of PEDF-Expressing Primary Pigment Epithelial Cells by the SB Transposon System Delivered by pFAR4 Plasmids.

Thumann G, Harmening N, Prat-Souteyrand C, Marie C, Pastor M, Sebe A, Miskey C, Hurst LD, Diarra S, Kropp M, Walter P, Scherman D, Ivics Z, Izsvák Z, Johnen S.

Abstract: Neovascular age-related macular degeneration (nvAMD) is characterized by choroidal blood vessels growing into the subretinal space, leading to retinal pigment epithelial (RPE) cell degeneration and vision loss. Vessel growth results from an imbalance of pro-angiogenic (e.g., vascular endothelial growth factor [VEGF]) and anti-angiogenic factors (e.g., pigment epithelium-derived factor [PEDF]). Current treatment using intravitreal injections of anti-VEGF antibodies improves vision in about 30% of patients but

may be accompanied by side effects and non-compliance. To avoid the difficulties posed by frequent intravitreal injections, we have proposed the transplantation of pigment epithelial cells modified to overexpress human PEDF. Stable transgene integration and expression is ensured by the hyperactive Sleeping Beauty transposon system delivered by pFAR4 miniplasmids, which have a backbone free of antibiotic resistance markers. We demonstrated efficient expression of the PEDF gene and an optimized PEDF cDNA sequence in as few as 5×10^3 primary cells. At 3 weeks post-transfection, PEDF secretion was significantly elevated and long-term follow-up indicated a more stable secretion by cells transfected with the optimized PEDF transgene. Analysis of transgene insertion sites in human RPE cells showed an almost random genomic distribution. The results represent an important contribution toward a clinical trial aiming at a non-viral gene therapy of nvAMD.

PMID: 28325297

Genetics. 2017 Mar 24. [Epub ahead of print]

Bivariate Analysis of Age-Related Macular Degeneration Progression Using Genetic Risk Scores.

Ding Y, Liu Y, Yan Q, Fritsche LG, Cook RJ, Clemons T, Ratnapriya R, Klein ML, Abecasis GR, Swaroop A, Chew EY, Weeks DE, Chen W.

Abstract: Age-related macular degeneration (AMD) is a leading cause of blindness in the developed world. While many AMD susceptibility variants have been identified, their influence on AMD progression has not been elucidated. Using data from two large clinical trials, Age-Related Eye Disease Study (AREDS) and AREDS2, we evaluated the effects of 34 known risk variants on disease progression. In doing so, we calculated the eye-level time-to-late-AMD and modeled them using a bivariate survival analysis approach, appropriately accounting for between-eye correlation. We then derived a genetic risk score (GRS) based on these 34 risk variants, and analyzed its effect on AMD progression. Finally, we used the AREDS data to fit prediction models of progression based on demographic and environmental factors, eye-level AMD severity scores and the GRS and tested the models using the AREDS2 cohort. We observed that GRS was significantly associated with AMD progression in both cohorts, with a stronger effect in AREDS than in AREDS2 (AREDS: Hazard Ratio (HR) = 1.34, $p=1.6 \times 10^{-22}$; AREDS2: HR=1.11, $p=2.1 \times 10^{-4}$). For prediction of AMD progression, addition of GRS to the demographic/environmental risk factors considerably improved the prediction performance. However, when the baseline eye-level severity scores were included as the predictors, any other risk factors including the GRS only provided small additional predictive power. Our model for predicting the disease progression risk demonstrated satisfactory performance in both cohorts, and we recommend its use with baseline AMD severity scores plus baseline age, education level, smoking status, either with or without GRS.

PMID: 28341650

Clin Chem Lab Med. 2017 Mar 27. [Epub ahead of print]

miRNAs, single nucleotide polymorphisms (SNPs) and age-related macular degeneration (AMD).

SanGiovanni JP, SanGiovanni PM, Sapieha P, De Guire V.

Abstract: Advanced age-related macular degeneration (AAMD) is a complex sight-threatening disease of public health significance. Micro RNAs (miRNAs) have been proposed as biomarkers for AAMD. The presence of certain single nucleotide polymorphisms (SNPs) may influence the explanatory value of these biomarkers. Here we present findings from an integrated approach used to determine whether AAMD-associated SNPs have the capacity to influence miRNA-mRNA pairing and, if so, to what extent such pairing may be manifested in a discrete AAMD transcriptome. Using a panel of 8854 SNPs associated with AAMD at p -values $\leq 5.0 \times 10^{-7}$ from a cohort of >30,000 elderly people, we identified SNPs in miRNA target-

encoding constituents of: (1) regulator of complement activation (RCA) genes (rs390679, CFHR1, $p \leq 2.14 \times 10^{-214}$ | rs12140421, CFHR3, $p \leq 4.63 \times 10^{-29}$); (2) genes of major histocompatibility complex (MHC) loci (rs4151672, CFB, $p \leq 8.91 \times 10^{-41}$ | rs115404146, HLA-C, $p \leq 6.32 \times 10^{-12}$ | rs1055821, HLA-B, $p \leq 1.93 \times 10^{-9}$ | rs1063355, HLA-DQB1, $p \leq 6.82 \times 10^{-14}$); and (3) genes of the 10q26 AMD locus (rs1045216, PLEKHA1, $p \leq 4.17 \times 10^{-142}$ | rs2672603, ARMS2, $p \leq 7.14 \times 10^{-46}$). We used these findings with existing data on AMD-related retinal miRNA and transcript profiles for the purpose of making inferences on SNP-mRNA-miRNA-AMD relationships. Four of 12 miRNAs significantly elevated in AMD retina (hsa-miR-155-5p, hsa-let-7a-5p, hsa-let-7b-5p, hsa-let-7d-5p) also showed strong pairing capacity (TarBase 7.1 context++ score < -0.2 , miRanda 3.3 pairing score > 150) with miRNA target transcripts encoded by AMD-associated SNPs resident in HLA-DQB1 (rs1063355, hsa-miR-155-5p) and TGFB1 (rs868, hsa-let-7). Three of the 12 miRNAs overexpressed in AMD retina are inducible by NF κ B and have high affinity targets in the complement factor H (CFH) mRNA 3' UTR. We used ENSEMBL to identify polymorphic regions in the CFH mRNA 3' UTR with the capacity to disrupt miRNA-mRNA pairing. Two variants (rs76666504 and rs459598) existed in DNA sequence encoding the seed region of hsa-miR-146a-5p in the CFH mRNA 3' UTR - as this miRNA is also elevated in both vitreous and serum of people with AMD, it shows great value as a biomarker. Our findings suggest that knowledge on the nature of DNA sequence variation may increase the explanatory power of miRNA biomarkers in genetically diverse populations, while yielding information with which to develop: (1) mechanistic tests on processes implicated in AMD pathogenesis; and, (2) site-specific small molecules (synthetic mimetics or anti-miRNAs) with preventive or therapeutic efficacy for AMD.

PMID: 28343170

Hum Mol Genet. 2017 Feb 22. [Epub ahead of print]

DAPL1, a susceptibility locus for age-related macular degeneration, acts as a novel suppressor of cell proliferation in the retinal pigment epithelium.

Ma X, Li H, Wang Y, Wang J, Zheng Q, Hua J, Yang J, Pan L, Lu F, Qu J, Hou L.

Abstract: The retinal pigment epithelium (RPE) forms a monolayer at the back of the vertebrate eye and is fundamental to retinal function and homeostasis. During early development, RPE cells undergo rapid proliferation, but in the adult, they remain normally nonproliferative throughout life. Nevertheless, under pathological conditions such as in proliferative vitreoretinopathy or after retinal ablation, mature RPE cells can re-enter the cell cycle and form nodules or multiple cell layers. Here we show that Dapl1, whose human homolog represents a susceptibility locus for age-related macular degeneration (AMD), is highly up-regulated in quiescent but not proliferating RPE cells and that experimental overexpression of DAPL1 in proliferating RPE cells inhibits their proliferation. Consistent with this observation, the percent of Ki67-positive cells is significantly higher in E11.5 Dapl1 knockout mouse embryos compared to age-matched controls. In adult Dapl1 $^{-/-}$ mice, which survive without showing any overt pathology, RPE overgrowth leads to multiple cell layers and/or cellular nodules. The antiproliferative effect of DAPL1 is associated with an increase in CDKN1A protein levels. Reduction of CDKN1A by siRNA in DAPL1-overexpressing RPE cells in vitro partially restores cell proliferation. Hence, we show that DAPL1 is a novel regulator of RPE cell proliferation that is important for the maintenance of the RPE as a monolayer. The findings suggest that DAPL1 dysregulation may be involved in abnormal RPE-related proliferative diseases and corresponding retinal dysfunctions in humans.

PMID: 28334846

Exp Cell Res. 2017 Mar 16. [Epub ahead of print]

HIF signalling: The eyes have it.

Peet DJ, Kittipassorn T, Wood JP, Chidlow G, Casson RJ.

Abstract: The hypoxia inducible factors (HIFs) promote changes in gene expression in response to hypoxia, and mediate key physiological responses such as angiogenesis. They play important roles in development and normal physiology, as well as in ischaemic and other pathologies. The human eye is a complex organ, with tight regulation of vascularisation and oxygen delivery, with the highly specialised retina containing both highly vascularised and avascular regions. This review, written to honour the significant contribution of Lorenz Poellinger to this field, covers the role of the HIFs in normal development of the eye, specifically the vasculature, as well as their roles in numerous retinal pathologies, including ischaemic retinopathies, and age-related macular degeneration (AMD). The characterisation of the HIFs in the eye has improved our understanding of the development, function, and numerous pathologies of the eye, and should inform future therapeutic approaches.

PMID: 28315667

Stem cells

Cell Transplant. 2017 Mar 17. [Epub ahead of print]

Perspectives of Stem Cell-Based Therapy for Age-Related Retinal Degenerative Diseases.

Holan V, Hermankova B, Koss J.

Abstract: Retinal degenerative diseases, which include age-related macular degeneration, retinitis pigmentosa, diabetic retinopathy and glaucoma, mostly affect the elderly population, and are the most common cause of decreased quality of vision or even blindness. So far, there is no satisfactory treatment protocol to prevent, stop or cure these disorders. A great hope and promise for patients suffering from retinal diseases is represented by stem cell-based therapy which could replace diseased or missing retinal cells, and support regeneration. In this respect, mesenchymal stem cells (MSCs) which can be obtained from the particular patient, and used as autologous cells, have turned out to be a promising stem cell type for treatment. Here we show that MSCs can differentiate into cells expressing markers of retinal cells, inhibit production of proinflammatory cytokines by retinal tissue and produce a number of growth and neuroprotective factors for retinal regeneration. All of these properties make MSCs a prospective cell type for cell-based therapy of age-related retinal degenerative diseases.

PMID: 28315291

Mol Ther. 2017 Mar 15. [Epub ahead of print]

Cell Therapy for Age-Related Macular Degeneration: A New Vision for the Bone Marrow?

Ljubimov AV.

PMID: 28318930

Diet, lifestyle and low vision

Ophthalmic Epidemiol. 2017 Mar 23:1-12. [Epub ahead of print]

Association between Dietary Xanthophyll (Lutein and Zeaxanthin) Intake and Early Age-Related Macular Degeneration: The Atherosclerosis Risk in Communities Study.

Lin H, Mares JA, LaMonte MJ, Brady WE, Sahli MW, Klein R, Klein BE, Nie J, Millen AE.

PURPOSE: To examine the association between xanthophyll intake and prevalent early age-related macular degeneration (AMD) using data from the Atherosclerosis Risk in Communities Study (n = 10,295). Potential effect modification by genetic polymorphisms and biomarkers of high-density lipoprotein (HDL) metabolism was explored.

METHODS: Xanthophyll intake was assessed at visit 1 (1987-1989) using food frequency questionnaires. Prevalent early AMD was assessed at visit 3 (1993-1995) via retinal photographs. Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for AMD by quintiles of xanthophyll intake, adjusted for age, sex, race, field center, and pack-years of smoking. To evaluate effect modification, the association between tertiles (T) of xanthophyll intake and AMD was stratified by complement factor H (CFH) rs1061170 and age-related maculopathy susceptibility 2 (ARMS2) rs10490924 genotypes, as well as by median cutpoints of HDL biomarkers.

RESULTS: Xanthophyll intake was not associated with AMD in the overall sample, Caucasians (n = 8257), or African-Americans (n = 2038). Exploratory analyses observed that the association between xanthophyll intake and AMD varied statistically significantly by CFH rs1061170 genotype among Caucasians (p for interaction = 0.045) but not African Americans. No interactions were observed between xanthophyll intake and ARMS2 rs10490924. Moreover, higher xanthophyll intake was associated with decreased odds of AMD among participants with lower HDL (OR = 0.79, 95% CI 0.57-1.09) but not higher HDL (p for interaction = 0.048).

CONCLUSION: Xanthophyll intake was not associated with early AMD. Further studies to investigate this association by genetic susceptibility or variations in HDL metabolism are needed.

PMID: 28332910

J Fr Ophtalmol. 2017 Mar 20. [Epub ahead of print]

Macular pigment density variation after supplementation of lutein and zeaxanthin using the Visucam® 200 pigment module: Impact of age-related macular degeneration and lens status.

Azar G, Quaranta-El Maftouhi M, Masella JJ, Mauget-Faÿsse M.

PURPOSE: To assess the evolution of macular pigment optical density (MPOD) following supplementation with various macular formulations obtained with the Visucam® 200, and to study the factors affecting MPOD measurements.

MATERIALS AND METHODS: In this prospective, randomized, double-masked multicenter study, patients were divided into 2 groups: group A (patients without retinal pathology who underwent cataract surgery 1 month previously) and group B (patients with neovascular age-related macular degeneration [AMD] in one eye). In each group, half of the patients were randomly assigned to receive a food supplementation either with or without carotenoids (5mg of Lutein and 1mg of Zeaxanthin). Outcome measures included MPOD responses obtained with the Visucam® 200 for one year.

RESULTS: In total, 126 subjects (52 men, 74 women) with a mean age of 75.3±7.61 years were enrolled. Mean MPOD values at the time of inclusion were statistically lower in group A (0.088 density unit [DU]) compared to group B (0.163 DU, P<0.05). No statistically significant increase in MPOD was noted in either group, even after discontinuation of the supplementation. By multiple regression analysis, age, female gender, lens status and the presence of AMD seemed to significantly affect MPOD measurements.

CONCLUSION: No significant improvement in MPOD seems to be detected with the Visucam® 200 after carotenoid supplementation. The MPOD measurement seems to be highly affected by cataract extraction and the presence of AMD.

PMID: 28336284

Prog Retin Eye Res. 2017 Mar 20. [Epub ahead of print]

The impact of oxidative stress and inflammation on RPE degeneration in non-neovascular AMD.

Datta S, Cano M, Ebrahimi K, Wang L, Handa JT.

Abstract: The retinal pigment epithelium (RPE) is a highly specialized, unique epithelial cell that interacts with photoreceptors on its apical side and with Bruch's membrane and the choriocapillaris on its basal side. Due to vital functions that keep photoreceptors healthy, the RPE is essential for maintaining vision. With aging and the accumulated effects of environmental stresses, the RPE can become dysfunctional and die. This degeneration plays a central role in age-related macular degeneration (AMD) pathobiology, the leading cause of blindness among the elderly in western societies. Oxidative stress and inflammation have both physiological and potentially pathological roles in RPE degeneration. Given the central role of the RPE, this review will focus on the impact of oxidative stress and inflammation on the RPE with AMD pathobiology. Physiological sources of oxidative stress as well as unique sources from photo-oxidative stress, the phagocytosis of photoreceptor outer segments, and modifiable factors such as cigarette smoking and high fat diet ingestion that can convert oxidative stress into a pathological role, and the negative impact of impairing the cytoprotective roles of mitochondrial dynamics and the Nrf2 signaling system on RPE health in AMD will be discussed. Likewise, the response by the innate immune system to an inciting trigger, and the potential role of local RPE production of inflammation, as well as a potential role for damage by inflammation with chronicity if the inciting trigger is not neutralized, will be debated.

PMID: 28336424

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