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MD Research News

Issue 282

Monday 6 June, 2016

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Drug treatment

Korean J Ophthalmol. 2016 Jun;30(3):192-7. doi: 10.3341/kjo.2016.30.3.192. Epub 2016 May 18.

Management of Acute Submacular Hemorrhage with Intravitreal Injection of Tenecteplase, Anti-vascular Endothelial Growth Factor and Gas.

Lee JP, Park JS, Kwon OW, You YS, Kim SH.

PURPOSE: To evaluate the visual and anatomical outcomes for neovascular age-related macular degeneration with submacular hemorrhage after intravitreal injections of tenecteplase (TNK), anti-vascular endothelial growth factor (VEGF) and expansile gas.

METHODS: This study was a retrospective clinical case series following 25 eyes of 25 patients. All patients received a triple injection using 0.05 mL TNK (50 μg), 0.05 mL anti-VEGF and 0.3 mL of perfluoropropane gas. Retreatment with anti-VEGF was performed as needed. Preoperative and postoperative best-corrected visual acuity and central retinal thickness were analyzed.

RESULTS: The mean logarithm of the minimum angle of resolution of best-corrected visual acuity improved significantly from 1.09 ± 0.77 at baseline to 0.52 ± 0.60 at 12 months ($p < 0.001$). The mean central retinal thickness also improved significantly from 545 ± 156 at baseline to 266 ± 107 at 12 months ($p < 0.001$). A visual improvement of 0.3 logarithm of the minimum angle of resolution unit or more was achieved in 15 eyes (60%). During the 12 postoperative months, an average of 4.04 intravitreal anti-VEGF injections was applied.

CONCLUSIONS: A triple injection of TNK, anti-VEGF, and a gas appears to be safe and effective for the treatment of submacular hemorrhage secondary to neovascular age-related macular degeneration.

PMID: 27247518 [PubMed - in process] PMCID: PMC4878979

Ophthalmology. 2016 May 25. [Epub ahead of print]

Enhanced Benefit in Diabetic Macular Edema from AKB-9778 Tie2 Activation Combined with Vascular Endothelial Growth Factor Suppression.

Campochiaro PA, Khanani A, Singer M, Patel S, Boyer D, Dugel P, Kherani S, Withers B, Gambino L, Peters K, Brigell M; TIME-2 Study Group.

PURPOSE: To assess the effect of AKB-9778 alone or in combination with ranibizumab in subjects with diabetic macular edema (DME).

DESIGN: A phase IIa, randomized, placebo- and sham injection-controlled, double-masked clinical trial.

PARTICIPANTS: Subjects (n = 144) with decreased vision from DME and central subfield thickness (CST) ≥325 μm measured by spectral-domain optical coherence tomography (SD OCT) enrolled at 36 sites.

METHODS: Subjects were randomized to (1) AKB-9778 monotherapy: subcutaneous AKB-9778 15 mg twice per day (BID) + monthly sham intraocular injections; (2) combination therapy: subcutaneous AKB-9778 15 mg BID + monthly 0.3 mg ranibizumab; or (3) ranibizumab monotherapy: subcutaneous placebo injections BID + monthly 0.3 mg ranibizumab. Best-corrected visual acuity (BCVA) and CST were measured at baseline and every 4 weeks.

MAIN OUTCOME MEASURES:

Primary outcome measure was mean change from baseline CST at week 12. Other outcomes included BCVA, safety assessments, and Diabetic Retinopathy Severity Score (DRSS).

RESULTS: At week 12, mean change from baseline CST was significantly greater in the combination group (-164.4±24.2 μm) compared with the ranibizumab monotherapy group (-110.4±17.2 μm; P = 0.008) and was 6.2±13.0 μm in the AKB-9778 monotherapy group. Mean CST at week 12 and percentage of eyes with resolved edema was 340.0±11.2 μm and 29.2%, respectively, in the combination group versus 392.1±17.1 μm and 17.0%, respectively, in the ranibizumab monotherapy group. Mean change from baseline BCVA (letters) was 6.3±1.3 in the combination group, 5.7±1.2 in the ranibizumab monotherapy group, and 1.5±1.2 in the AKB-9778 monotherapy group. The percentage of study eyes that gained ≥10 or ≥15 letters was 8.7% and 4.3%, respectively, in the AKB-9778 monotherapy group, 29.8% and 17.0%, respectively, in the ranibizumab monotherapy group, and 35.4% and 20.8%, respectively, in the combination group. Improvements in DRSS in study eyes were similar across groups, and the percentage of qualified fellow eyes with a ≥2-step change was 11.4% in all AKB-9778-treated subjects compared with 4.2% in the ranibizumab monotherapy group. AKB-9778 was well tolerated, with no clear by-treatment differences in adverse events.

CONCLUSIONS: Activation of Tie2 by subcutaneous injections of AKB-9778 combined with suppression of vascular endothelial growth factor (VEGF) causes a significantly greater reduction in DME than that seen with suppression of VEGF alone.

PMID: 27236272 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2016 Jun 2. [Epub ahead of print]

Comparison of intravitreal aflibercept and ranibizumab injections on subfoveal and peripapillary choroidal thickness in eyes with neovascular age-related macular degeneration.

Uzun S, Pehlivan E.

PMID: 27251193 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Retina. 2016 May 27. [Epub ahead of print]

EFFECTIVENESS OF DIFFERENT MONITORING MODALITIES IN THE DETECTION OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: The Home Study, Report Number 3.

Chew EY, Clemons TE, Harrington M, Bressler SB, Elman MJ, Kim JE, Garfinkel R, Heier JS, Brucker A, Boyer D; AREDS2-HOME Study Research Group.

PURPOSE: To determine the effectiveness of different monitoring modalities to detect incident neovascularization associated with age-related macular degeneration (AMD).

METHODS: Secondary analyses compared the rates of detecting incident neovascular AMD in prescheduled office visits versus office visits triggered by monitoring device or by symptom realization in a randomized trial evaluating home telemonitoring device plus standard care (device arm) versus standard care alone.

RESULTS: At prescheduled office visits, neovascular AMD was detected in 14/1927 visits (0.7%, 95% confidence interval [CI]: 0.4%-1.1%) and 14/1949 visits (0.7%, 95% CI: 0.3%-1.1%) in the device and standard care alone arms, respectively. Thirty-seven participants with neovascular AMD were detected in 318 office visits (11.6%, 95% CI: 8.1%-15.2%) triggered by device or symptom realization and 17 neovascular AMD in 65 office visits (26%, 95% CI: 15.5%-36.8%) triggered by symptom realization in the device and standard care alone arms, respectively. The home device strategy had a higher neovascular-AMD detection rate than prescheduled office visits (relative risk = 16.0 [95% CI: 8.8-29.3]). Neovascular AMD detected at triggered visits were associated with less vision loss from baseline in the device arm versus standard care alone arm (-3 letters vs. -11.5 letters, respectively, P = 0.03).

CONCLUSION: Telemonitoring may alter the management of patients with AMD and improve vision outcomes.

PMID: 27243927 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2016 Jun 3. [Epub ahead of print]

Cataract surgery in patients with neovascular age-related macular degeneration.

Kessel L, Koefoed Theil P, Lykke Sørensen T, Munch IC.

PURPOSE: To examine the outcome after cataract surgery in patients with neovascular age-related macular degeneration (AMD) treated with intravitreal anti-vascular endothelial growth factor (VEGF) injections in routine clinical practice.

METHODS: We extracted information about patients recorded in electronic databases managing anti-VEGF injections and cataract surgery. We compared Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity and frequency of anti-VEGF injections before and after cataract surgery.

RESULTS: We identified 89 eyes from 89 patients who had cataract surgery after being treated with a median of 10 (range 3-36) anti-VEGF injections for neovascular AMD. Visual acuity improved by a mean of 7.1 [95% confidence interval (CI) 4.6-9.6] ETDRS letters in the first 6 months after cataract surgery. The need of anti-VEGF injections did not change after cataract surgery with an average of 1.5 in the 6 months before surgery versus 1.7 in the 6 months after surgery (p = 0.25). Visual improvement was greater in patients when the time from latest injection to cataract surgery was lower.

CONCLUSIONS: Cataract surgery improves vision in patients undergoing treatment for neovascular AMD. Cataract surgery was not associated with an increased need for anti-VEGF treatment and patients who were in active anti-VEGF treatment had better visual outcomes than patients who had cataract surgery after long injection-free periods.

PMID: 27255691 [PubMed - as supplied by publisher]

Curr Eye Res. 2016 Jun 3:1-6. [Epub ahead of print]

A Novel Tool for the Assessment Oxidative Stress in Age-Related Macular Degeneration: Thiol/ Disulfide Homeostasis Revisited.

Arıkan Yorgun M, Toklu Y, Altınkaynak H, Tanrıverdi B, Ergin M, Biçer C.

PURPOSE: To investigate thiol/disulfide status using a novel automated assay in patients with age-related macular degeneration (AMD) compared to age-matched healthy controls.

METHODS: A total of 64 AMD patients [51 (79%) non-exudative, 13 (21%) exudative AMD] and 21 age-matched healthy control subjects were enrolled in this study. Plasma total thiol, native thiol, disulfide levels were measured and native thiol/disulfide ratio (TDR) was calculated using a novel spectrophotometric assay.

RESULTS: Patients with AMD had significantly lower levels of total thiol (434.8 ± 7.0 μmol/L vs. 472.2 ± 7.9 μmol/L, p < 0.001), native thiol (393.6 ± 6.5 μmol/L vs. 437.5 ± 7.1 μmol/L, p = 0.004) compared to healthy controls. However, plasma disulfide levels were higher in AMD patients (20.6 ± 0.9 μmol/L vs. 17.3 ± 1.3 μmol/L, p = 0.113) compared to healthy controls. The TDR was not statistically different between the early AMD group and healthy controls (24.2 ± 2.3 vs. 29.5 ± 3.1, p = 0.345). However, intermediate and advanced stage AMD groups had significantly lower levels of TDR compared to healthy controls (21.6 ± 2.6 vs. 29.5 ± 3.1, p = 0.023 and 20.3 ± 1.2 vs. 29.5 ± 3.1, p = 0.005, respectively). Native TDR was significantly lower in patients with exudative and non-exudative AMD (19.9 ± 2.3 vs. 29.5 ± 3.1, p = 0.024 and 21.8 ± 1.14 vs. 29.47 ± 3.1 respectively, p = 0.011).

CONCLUSION: A greater extent of thiol consumption occurred in AMD patients compared to age-matched healthy controls. However, despite the similar levels of total thiol levels between several grades of AMD, the plasma native TDR value was decreased in accordance with the severity of the disease, which reflected the disease grade better.

PMID: 27261249 [PubMed - as supplied by publisher]

JAMA Ophthalmol. 2016 Jun 2. [Epub ahead of print]

Microperimetry Features of Geographic Atrophy Identified With En Face Optical Coherence Tomography.

Pilotto E, Convento E, Guidolin F, Abalsamo CK, Longhin E, Parrozzani R, Midena E.

IMPORTANCE: Progressive geographic atrophy (GA) of the retinal pigment epithelium leads to loss of central vision. To identify GA in age-related macular degeneration and assess treatment, correlation of function observed on microperimetry with structure observed on optical coherence tomographic (OCT) images may be of value.

OBJECTIVE: To characterize the microperimetric function of GA as identified from en face OCT imaging.

DESIGN, SETTING, AND PARTICIPANTS: In a case-series study, 20 patients (22 eyes) entered the study at the University of Padova according to preplanned conditions. From March 1 to July 30, 2014, en face OCT images were obtained at the outer retinal layer and choroidal layer levels. The microperimetry sensitivity map was superimposed on the en face OCT images, which had been used to measure GA areas. Relative and dense scotoma rates were calculated in the GA areas. After data collection, the study eyes were divided into 3 groups according to the macular residual mean sensitivity.

MAIN OUTCOMES AND MEASURES: Retinal sensitivity measured by microperimetry within areas of GA identified by en face OCT images.

RESULTS: Twenty patients (5 men and 15 women) were included in the study, with a mean (SD) age of 79.5 (7.0) years (range, 69-98 years). Macular residual mean retinal sensitivity was less than 5 dB in 7 eyes (group 1), 5 to 10 dB in 9 eyes (group 2), and greater than 10 dB in 6 eyes (group 3). Mean (SD) GA area differed among the groups at the outer retinal (13.13 [5.03] mm2 [range, 5.75-21.04 mm2] in group 1; 7.80 [3.25] mm2 [range, 3.31-13.52 mm2] in group 2; and 3.94 [2.35] mm2 [range, 1.46-7.90 mm2] in group 3; P = .001) and choroidal (11.83 [5.55] mm2 [range, 4.55-22.14 mm2] in group 1; 7.00 [4.29] mm2 [range, 0.90-13.83 mm2] in group 2; and 3.27 [2.29] mm2 [range, 0.91-7.23 mm2] in group 3; P = .007) layer levels. Mean (SD) GA area imaged at the outer retinal layer level was significantly larger than that imaged at the choroidal level in group 3 (difference, 0.67 mm2; 95% CI, 0.31-1.03 mm2; P = .005), but not in groups 1 or 2. Mean (SD) rate of relative scotoma was significantly higher in the GA area imaged at the outer retinal layer level than at the choroidal level in group 3 (47.70% [31.30%] [range, 13.60%-100%] vs 34.00% [37.30%] [range, 0%-100%]; difference, 13.74%; 95% CI, 3.84%-23.63%; P = .02), but not in groups 1 or 2.

CONCLUSIONS AND RELEVANCE: In the early stage of GA, when retinal sensitivity is relatively good, these data suggest that the GA area imaged on en face OCT at the outer retinal level correctly detects the wide functional degenerative involvement of the photoreceptors. These findings provide novel data that correlate function and structure, which may be of value when assessing treatments that might prevent or

reduce the rate of growth of GA.

PMID: 27253760 [PubMed - as supplied by publisher]

Comput Biol Med. 2016 May 17;75:54-62. [Epub ahead of print]

Automated screening system for retinal health using bi-dimensional empirical mode decomposition and integrated index.

Acharya UR, Mookiah MR, Koh JE, Tan JH, Bhandary SV, Rao AK, Fujita H, Hagiwara Y, Chua CK, Laude A.

Abstract: Posterior Segment Eye Diseases (PSED) namely Diabetic Retinopathy (DR), glaucoma and Age-related Macular Degeneration (AMD) are the prime causes of vision loss globally. Vision loss can be prevented, if these diseases are detected at an early stage. Structural abnormalities such as changes in cup-to-disc ratio, Hard Exudates (HE), drusen, Microaneurysms (MA), Cotton Wool Spots (CWS), Haemorrhages (HA), Geographic Atrophy (GA) and Choroidal Neovascularization (CNV) in PSED can be identified by manual examination of fundus images by clinicians. However, manual screening is labour-intensive, tiresome and time consuming. Hence, there is a need to automate the eye screening. In this work Bi-dimensional Empirical Mode Decomposition (BEMD) technique is used to decompose fundus images into 2D Intrinsic Mode Functions (IMFs) to capture variations in the pixels due to morphological changes. Further, various entropy namely Renyi, Fuzzy, Shannon, Vajda, Kapur and Yager and energy features are extracted from IMFs. These extracted features are ranked using Chernoff Bound and Bhattacharyya Distance (CBBD), Kullback-Leibler Divergence (KLD), Fuzzy-minimum Redundancy Maximum Relevance (FmRMR), Wilcoxon, Receiver Operating Characteristics Curve (ROC) and t-test methods. Further, these ranked features are fed to Support Vector Machine (SVM) classifier to classify normal and abnormal (DR, AMD and glaucoma) classes. The performance of the proposed eye screening system is evaluated using 800 (Normal=400 and Abnormal=400) digital fundus images and 10-fold cross validation method. Our proposed system automatically identifies normal and abnormal classes with an average accuracy of 88.63%, sensitivity of 86.25% and specificity of 91% using 17 optimal features ranked using CBBD and SVM-Radial Basis Function (RBF) classifier. Moreover, a novel Retinal Risk Index (RRI) is developed using two significant features to distinguish two classes using single number. Such a system helps to reduce eye screening time in polyclinics or community-based mass screening. They will refer the patients to main hospitals only if the diagnosis belong to the abnormal class. Hence, the main hospitals will not be unnecessarily crowded and doctors can devote their time for other urgent cases.

PMID: 27253617 [PubMed - as supplied by publisher]

JAMA Ophthalmol. 2016 Jun 2. [Epub ahead of print]

Quantitative Fundus Autofluorescence in Early and Intermediate Age-Related Macular Degeneration.

Gliem M, Müller PL, Finger RP, McGuinness MB, Holz FG, Charbel Issa P.

IMPORTANCE: Increased lipofuscin accumulation is assumed to be an important factor in the pathogenesis of age-related macular degeneration (AMD), although direct evidence for this hypothesis is missing.

OBJECTIVE: To quantitatively investigate lipofuscin-associated fundus autofluorescence (AF) in patients with early and intermediate AMD.

DESIGN, SETTING, AND PARTICIPANTS: A prospective, single-center, case-control study was conducted from August 1, 2014, to October 31, 2015, at a university referral center. Participants included 40 patients aged 65 years or younger and 108 individuals without eye disease serving as controls. All participants underwent quantitative fundus AF (qAF) imaging with a modified scanning laser ophthalmoscope equipped with an internal fluorescent reference. Mean qAF values of an 8-segment circular ring centered on the

fovea (qAF8) were measured and compared between patients and controls. For subgroup analysis, drusen were categorized as soft drusen, cuticular drusen, and/or reticular pseudodrusen (RPD).

MAIN OUTCOMES AND MEASURES: The qAF8 levels.

RESULTS: In the 40 patients with AMD, mean (SD) age was 54.8 (5.6) years, and 32 (80%) were women. None of the investigated patients had qAF8 values above the 95% prediction interval (PI) of the 108 controls. In the soft drusen (28 [70%]) and cuticular drusen (8 [20%]) groups, qAF8 levels within the 95% PI were noted in 22 patients (79%; 95% CI, 60% to 90%) and 7 patients (88%; 95% CI, 51% to 99%) respectively. The qAF8 values in the RPD group (4 [10%]) were below the 95% PI in 3 patients (75%; 95% CI, 29% to 97%). Compared with the controls, statistical analysis revealed lower qAF8 values in the overall AMD cohort after adjusting for age (difference, -19.9% [95% CI, -25.6% to -12.7%], P < .001) as well as in all subgroups (soft drusen, -17.1% [95% CI, -24.1% to -9.5%], P < .001; cuticular drusen, -19.6% [95% CI, -30.3% to -7.2%], P = .003; and RPD, -34.5% [95% CI, -47.1% to -21.3%]; P < .001).

CONCLUSIONS AND RELEVANCE: The qAF8 measurements in this sample showed no increased lipofuscin-related fundus AF in patients with early and intermediate AMD. Lower qAF levels in certain subgroups may point to subnormal lipofuscin levels in the retinal pigment epithelium or, alternatively, limitations to detection of true retinal pigment epithelial lipofuscin content. The results of this study might expand the understanding of the pathogenesis of AMD and may have an effect on upcoming treatment trials that aim to modify lipofuscin accumulation.

PMID: 27253610 [PubMed - as supplied by publisher]

Exp Eye Res. 2016 May 31. [Epub ahead of print]

Murine fundus fluorescein angiography: An alternative approach using a handheld camera.

Ehrenberg M, Ehrenberg S, Schwob O, Benny O.

Abstract: In today's modern pharmacologic approach to treating sight-threatening retinal vascular disorders, there is an increasing demand for a compact, mobile, lightweight and cost-effective fluorescein fundus camera to document the effects of antiangiogenic drugs on laser-induced choroidal neovascularization (CNV) in mice and other experimental animals. We have adapted the use of the Kowa Genesis Df Camera to perform Fundus Fluorescein Angiography (FFA) in mice. The 1 kg, 28 cm high camera has built-in barrier and exciter filters to allow digital FFA recording to a Compact Flash memory card. Furthermore, this handheld unit has a steady Indirect Lens Holder that firmly attaches to the main unit, that securely holds a 90 diopter lens in position, in order to facilitate appropriate focus and stability, for photographing the delicate central murine fundus. This easily portable fundus fluorescein camera can effectively record exceptional central retinal vascular detail in murine laser-induced CNV, while readily allowing the investigator to adjust the camera's position according to the variable head and eye movements that can randomly occur while the mouse is optimally anesthetized. This movable image recording device, with efficiencies of space, time, cost, energy and personnel, has enabled us to accurately document the alterations in the central choroidal and retinal vasculature following induction of CNV, implemented by argon-green laser photocoagulation and disruption of Bruch's Membrane, in the experimental murine model of exudative macular degeneration.

PMID: 27260483 [PubMed - as supplied by publisher]

Korean J Ophthalmol. 2016 Jun;30(3):198-205. Epub 2016 May 18.

Optical Coherence Tomography-based Diagnosis of Polypoidal Choroidal Vasculopathy in Korean Patients.

Chang YS, Kim JH, Kim JW, Lee TG, Kim CG.

PURPOSE: To evaluate the efficacy of an optical coherence tomography (OCT)-based diagnosis of

polypoidal choroidal vasculopathy (PCV) in Korean patients.

METHODS: This retrospective, observational case series included 263 eyes of 263 patients (147 eyes with PCV and 116 eyes with typical exudative, age-related macular degeneration [AMD]) who had been diagnosed with treatment naïve exudative AMD. Eyes with three or more of the following OCT findings were diagnosed with PCV: multiple retinal pigment epithelial detachment (RPED), a sharp RPED peak, an RPED notch, a hyporeflective lumen representing polyps, and hyperreflective intraretinal hard exudates. The OCT-based diagnosis was compared with the gold-standard indocyanine green angiography-based method. The sensitivity and specificity of the OCT-based diagnosis was also estimated. An additional analysis was performed using a choroidal thickness criterion. Eyes with a subfoveal choroidal thickness greater than 300 µm were also diagnosed with PCV despite having only two OCT features.

RESULTS: In eyes with PCV, three or more OCT features were observed in 126 of 147 eyes (85.7%), and the incidence of typical exudative AMD was 16 of 116 eyes (13.8%). The sensitivity and specificity of an OCT-based diagnosis were 85.7% and 86.2%, respectively. After applying the choroidal thickness criterion, the sensitivity increased from 85.7% to 89.8%, and the specificity decreased from 86.2% to 84.5%.

CONCLUSIONS: The OCT-based diagnosis of PCV showed a high sensitivity and specificity in Korean patients. The addition of a choroidal thickness criterion improved the sensitivity of the method with a minimal decrease in its specificity.

PMID: 27247519 [PubMed - in process] PMCID: PMC4878980

JAMA Ophthalmol. 2016 Jun 2. [Epub ahead of print]

New Understanding of Age-Related Macular Degeneration Through Quantitative Autofluorescence.

Smith RT.

PMID: 27254789 [PubMed - as supplied by publisher]

Pathogenesis

Retina. 2016 Jun 2. [Epub ahead of print]

HYPERREFLECTIVE FOCI AS AN INDEPENDENT VISUAL OUTCOME PREDICTOR IN MACULAR EDEMA DUE TO RETINAL VASCULAR DISEASES TREATED WITH INTRAVITREAL DEXAMETHASONE OR RANIBIZUMAB.

Chatziralli IP1, Sergentanis TN, Sivaprasad S.

PURPOSE: To evaluate the potential role of hyperreflective foci (HF) in predicting visual outcome in patients undergoing treatment for macular edema due to retinal vascular diseases.

METHODS: Data and images of 92 patients with macular edema due to diabetes mellitus or branch retinal vein occlusion, treated with either intravitreal dexamethasone implant or ranibizumab, were analyzed. All patients underwent best-corrected visual acuity measurement, slit-lamp examination, spectral domain optical coherence tomography at baseline and at all time points of the follow-up (Month 1, 2, 3, 6, and 9). Generalized least squares random effects linear or logistic regression analysis was used to investigate potential factors associated with the final best-corrected visual acuity and number of HF, respectively.

RESULTS: Increasing age ($P < 0.001$), central retinal thickness ($P < 0.001$), number of HF ($P = 0.028$), presence of subretinal fluid ($P < 0.001$), intraretinal fluid ($P < 0.001$), intraretinal cysts ($P < 0.001$), and disruption of ellipsoid zone/external limiting membrane ($P < 0.001$) were significantly associated with poorer visual outcome. Factors associated with HF were increasing central retinal thickness ($P = 0.003$), presence of subretinal fluid ($P = 0.049$), intraretinal fluid ($P = 0.002$), cysts ($P = 0.015$), and disruption of ellipsoid zone ($P = 0.047$). No significant differences in change in best-corrected visual acuity, central retinal

thickness, and HF were observed between the two treatment groups.

CONCLUSION: Hyperreflective foci are associated with poorer visual outcome in patients with macular edema due to retinal vascular diseases. Similar reductions in HF are achieved by intravitreal steroid and anti-vascular endothelial growth factor agent.

PMID: 27258668 [PubMed - as supplied by publisher]

Exp Eye Res. 2016 May 30. [Epub ahead of print]

Method development to quantify Bv8 expression in circulating CD11b+ cells in patients with neovascular age-related macular degeneration (nvAMD) exhibiting Anti-VEGF refractoriness.

Catchpole T, Daniels T, Perkins J, Csaky KG.

Abstract: A subset of neovascular age-related macular degeneration (nvAMD) subjects appears to be refractory to the effects of anti-VEGF treatment and require frequent intravitreal injections. Prokineticin-2 (Bv8) expression in CD11b+ cells has been linked to anti-VEGF response. We have developed a reproducible method to quantify gene expression in circulating CD11b + cells. Utilizing this method we tested the hypothesis that high Bv8 expression in circulating CD11b+ cells is associated with anti-VEGF refractoriness in nvAMD patients. Two groups of nvAMD subjects undergoing treatment with anti-VEGF agents were recruited and classified as refractory or non-refractory to anti-VEGF treatment (n = 33 for each group). Two blood draws were obtained from each subject 1-9 months apart. Peripheral blood mononuclear cells (PBMCs) were isolated and CD11b+ cells were purified via magnetic bead separation. RNA was purified, and relative expression of Bv8 among the subjects was compared via quantitative PCR analysis. Utilizing this approach no significant difference was detected in the mean LogRQ values between the first and second blood draws (t-test, p = 0.826) indicating low intra-patient variability and demonstrating good reproducibility of the assay. There was no significant difference in Bv8 expression between nvAMD subjects classified as refractory versus non-refractory. We were unable to find a correlation between Bv8 expression in CD11b + cells and anti-VEGF refractoriness in human nvAMD subjects. Relatively high expression in Bv8 in these subjects did not correlate with clinical treatment history, as measured by the frequency of injections. Utilizing this well characterized technique, studies are underway to examine alternative gene expression profiles in various circulating cell populations that may contribute to anti-VEGF refractoriness.

PMID: 27256991 [PubMed - as supplied by publisher]

AIMS Mol Sci. 2016;3(2):196-221. Epub 2016 May 11.

Oxidative stress, innate immunity, and age-related macular degeneration.

Shaw PX, Stiles T, Douglas C, Ho D, Fan W, Du H, Xiao X.

Abstract: Age-related macular degeneration (AMD) is a leading cause of vision loss affecting tens of millions of elderly worldwide. Early AMD is characterized by the appearance of soft drusen, as well as pigmentary changes in the retinal pigment epithelium (RPE). These soft, confluent drusen can progress into two forms of advanced AMD: geographic atrophy (GA, or dry AMD) or choroidal neovascularization (CNV, or wet AMD). Both forms of AMD result in a similar clinical progression in terms of loss of central vision. The exact mechanism for developing early AMD, as well as triggers responsible for progressing to advanced stage of disease, is still largely unknown. However, significant evidence exists demonstrating a complex interplay of genetic and environmental factors as causes of AMD progression. Multiple genes and/or single nucleotide polymorphisms (SNPs) have been found associated with AMD, including various genes involved in the complement pathway, lipid metabolism and extracellular matrix (ECM) remodeling. Of the known genetic contributors to disease risk, the CFH Y402H and HTRA1/ARMS polymorphisms contribute to more than 50% of the genetic risk for AMD. Environmentally, oxidative stress plays a critical role in many aging diseases including cardiovascular disease, cancer, Alzheimer's disease and AMD. Due to the exposure to sunlight and high oxygen concentration, the oxidative stress burden is higher in the eye than

other tissues, which can be further complicated by additional oxidative stressors such as smoking. Increasingly, evidence is accumulating suggesting that functional abnormalities of the innate immune system incurred via high risk genotypes may be contributing to the pathogenesis of AMD by altering the inflammatory homeostasis in the eye, specifically in the handling of oxidation products. As the eye in non-pathological instances maintains a low level of inflammation despite the presence of a relative abundance of potentially inflammatory molecules, we have previously hypothesized that the tight homeostatic control of inflammation via the innate immune system is likely critical for avoidance of disease progression. However, the presence of a multitude of potential triggers of inflammation results in a sensitive balance in which perturbations thereof would subsequently alter the inflammatory state of the retina, leading to a state of chronic inflammation and pathologic progression. In this review, we will highlight the background literature surrounding the known genetic and environmental contributors to AMD risk, as well as a discussion of the potential mechanistic interplay of these factors that lead to disease pathogenesis with particular emphasis on the delicate control of inflammatory homeostasis and the centrality of the innate immune system in this process.

PMID: 27239555 [PubMed] PMCID: PMC4882104 Free PMC Article

Acta Histochem Cytochem. 2016 Apr 28;49(2):67-74. Epub 2016 Apr 9.

Hedgehog Signaling Components Are Expressed in Choroidal Neovascularization in Laser-induced Retinal Lesion.

Nochioka K, Okuda H, Tatsumi K, Morita S, Ogata N, Wanaka A.

Abstract: Choroidal neovascularization is one of the major pathological changes in age-related macular degeneration, which causes devastating blindness in the elderly population. The molecular mechanism of choroidal neovascularization has been under extensive investigation, but is still an open question. We focused on sonic hedgehog signaling, which is implicated in angiogenesis in various organs. Laser-induced injuries to the mouse retina were made to cause choroidal neovascularization. We examined gene expression of sonic hedgehog, its receptors (patched1, smoothened, cell adhesion molecule down-regulated by oncogenes (Cdon) and biregional Cdon-binding protein (Boc)) and downstream transcription factors (Gli1-3) using real-time RT-PCR. At seven days after injury, mRNAs for Patched1 and Gli1 were upregulated in response to injury, but displayed no upregulation in control retinas. Immunohistochemistry revealed that Patched1 and Gli1 proteins were localized to CD31-positive endothelial cells that cluster between the wounded retina and the pigment epithelium layer. Treatment with the hedgehog signaling inhibitor cyclopamine did not significantly decrease the size of the neovascularization areas, but the hedgehog agonist purmorphamine made the areas significantly larger than those in untreated retina. These results suggest that the hedgehog-signaling cascade may be a therapeutic target for age-related macular degeneration.

PMID: 27239075 [PubMed] PMCID: PMC4858541

Adv Exp Med Biol. 2016;917:261-85.

Inhibitors of Angiogenesis.

Büning H, Hacker UT.

Abstract: Angiogenesis plays a pivotal role in malignant, ischemic, inflammatory, infectious and immune disorders. The increasing molecular understanding of angiogenic processes fostered the development of strategies to induce or inhibit angiogenesis for therapeutic purposes. Here, we focus on anti-angiogenic therapies, which represent a standard of care in the treatment of different cancer types and in neovascular age-related macular degeneration. Specifically, strategies related to the blockade of angiogenic proteins and receptors will be outlined covering both preclinical and clinical aspects. Finally, examples of gene therapy based anti-angiogenic approaches are presented.

PMID: 27236560 [PubMed - in process]

Acta Ophthalmol. 2016 Jun 3. [Epub ahead of print]

Differential hypoxic response of human choroidal and retinal endothelial cells proposes tissue heterogeneity of ocular angiogenesis.

Mammadzada P, Gudmundsson J, Kvanta A, André H.

PURPOSE: To elaborate molecular differences between choroidal and retinal angiogenesis by generating and comparatively analysing human primary choroidal and retinal endothelial cell (CEC and REC) lines.

METHODS: Human CEC and REC were isolated by positive selection and were cultured. Characterization was performed by immunostaining for endothelial cell (EC)-specific markers. Total RNA and protein were extracted from normoxic or hypoxic CEC and REC cultures. Quantitative polymerase chain reaction (PCR) arrays were used to comparatively analyse 133 genes between CEC and REC, and the expression differences were calculated by ΔΔCt method. A total of 57 angiogenesis-related protein expression differences were investigated by Western blot and proteome profiler and were calculated by densitometry.

RESULTS: Primary human CEC and REC lines stained positively for all EC markers and demonstrated high purity with similar staining and morphology. Under normoxia, CEC showed significantly lower expression levels for cell proliferation and vessel maturation genes and higher expression levels for inflammation-related genes when compared to REC. In response to hypoxia, CEC and REC displayed differential regulation for a multitude of angiogenesis-related genes and proteins. Furthermore, within the vascular endothelial growth factor (VEGF) family, CEC showed preferential upregulation for vascular endothelial growth factor A (VEGFA) while REC upregulated placenta growth factor (PlGF) levels.

CONCLUSION: Differential normoxic and hypoxic regulation of angiogenesis-related factors by CEC and REC outlines tissue heterogeneity of ocular angiogenesis and suggests that tissue specificity should be considered as a novel treatment modality for successfully overcoming choroidal and retinal angiogenic conditions in the clinic.

PMID: 27255568 [PubMed - as supplied by publisher]

Sci Rep. 2016 May 31;6:26322.

Exogenous NAD(+) decreases oxidative stress and protects H2O2-treated RPE cells against necrotic death through the up-regulation of autophagy.

Zhu Y, Zhao KK, Tong Y, Zhou YL, Wang YX, Zhao PQ, Wang ZY.

Abstract: Increased oxidative stress, which can lead to the retinal pigment epithelium (RPE) cell death by inducing ATP depletion and DNA repair, is believed to be a prominent pathology in age-related macular degeneration (AMD). In the present study, we showed that and 0.1 mM nicotinamide adenine dinucleotide (NAD(+)) administration significantly blocked RPE cell death induced by 300 μM H2O2. Further investigation showed that H2O2 resulted in increased intracellular ROS level, activation of PARP-1 and subsequently necrotic death of RPE cells. Exogenous NAD(+) administration significantly decreased intracellular and intranuclear ROS levels in H2O2-treated RPE cells. In addition, NAD(+) administration to H2O2-treated RPE cells inhibited the activation of PARP-1 and protected the RPE cells against necrotic death. Moreover, exogenous NAD(+) administration up-regulated autophagy in the H2O2-treated RPE cells. Inhibition of autophagy by LY294002 blocked the decrease of intracellular and intranuclear ROS level. Besides, inhibition of autophagy by LY294002 abolished the protection of exogenous NAD(+) against H2O2 -induced cell necrotic death. Taken together, our findings indicate that that exogenous NAD(+) administration suppresses H2O2-induced oxidative stress and protects RPE cells against PARP-1 mediated necrotic death through the up-regulation of autophagy. The results suggest that exogenous NAD (+) administration might be potential value for the treatment of AMD.

PMID: 27240523 [PubMed - in process]

J Photochem Photobiol B. 2016 May 21;161:177-183. [Epub ahead of print]

Inflammasome priming increases retinal pigment epithelial cell susceptibility to lipofuscin phototoxicity by changing the cell death mechanism from apoptosis to pyroptosis.

Brandstetter C, Patt J, Holz FG, Krohne TU.

Abstract: Progressive death of retinal pigment epithelium (RPE) cells is a hallmark of age-related macular degeneration (AMD), the leading cause of blindness in all developed countries. Photooxidative damage and activation of the NLRP3 inflammasome have been suggested as contributing factors to this process. We investigated the effects of inflammasome activation on oxidative damage-induced RPE cell death. In primary human RPE cells and ARPE-19 cells, lipofuscin accumulated following incubation with oxidatively modified photoreceptor outer segments. Oxidative stress was induced by blue light irradiation (dominant wavelength: 448nm, irradiance: 0.8mW/cm2, duration: 3 to 6h) of lipofuscin-loaded cells and resulted in cell death by apoptosis. Prior inflammasome priming by IL-1α or complement activation product C5a altered the cell death mechanism to pyroptosis and resulted in a significant increase of the phototoxic effect. Following IL-1α priming, viability 24h after irradiation was reduced in primary RPE cells and ARPE-19 cells from 65.3% and 56.7% to 22.6% (p=0.003) and 5.1% (p=0.0002), respectively. Inflammasome-mediated IL-1β release occurred only in association with pyroptotic cell lysis. Inflammasome priming by conditioned media of pyroptotic cells likewise increased cell death. Suppression of inflammasome activation by inhibition of caspase-1 or cathepsins B and L significantly reduced cell death in primed cells. In summary, inflammasome priming by IL-1α, C5a, or conditioned media of pyroptotic cells increases RPE cell susceptibility to photooxidative damage-mediated cell death and changes the mechanism of induced cell death from apoptosis to pyroptosis. This process may contribute to RPE degeneration in AMD and provide new targets for intervention.

PMID: 27240191 [PubMed - as supplied by publisher]

Small GTPases. 2016 Jun 2:0. [Epub ahead of print]

Isoform-specific targeting of ROCK proteins in immune cells.

Zanin-Zhorov A, Flynn R, Waksal SD, Blazar BR.

Abstract: Rho-associated kinase 1 (ROCK1) and ROCK2 are activated by Rho GTPase and control cytoskeleton rearrangement through modulating the phosphorylation of their down-stream effector molecules. Although these two isoforms share more than 90% homology within their kinase domain the question of whether ROCK proteins function identically in different cell types is not clear. By using both pharmacological inhibition and genetic knockdown approaches recent studies suggest that the ROCK2 isoform plays an exclusive role in controlling of T-cell plasticity and macrophage polarization. Specifically, selective ROCK2 inhibition shifts the balance between pro-inflammatory and regulatory T-cell subsets via concurrent regulation of STAT3 and STAT5 phosphorylation, respectively. Furthermore, the administration of an orally available selective ROCK2 inhibitor effectively ameliorates clinical manifestations in experimental models of autoimmunity and chronic graft-versus-host disease (cGVHD). Because ROCK2 inhibition results in the suppression of M2-type macrophages while favoring polarization of M1-type macrophages, ROCK2 inhibition can correct the macrophage imbalance seen during age-related macular degeneration (AMD). In summary, the exclusive role of ROCK2 in immune system modulation argues for the development and testing of isoform-specific ROCK2 inhibitors for the treatment of inflammatory disorders.

PMID: 27254302 [PubMed - as supplied by publisher]

Sci Rep. 2016 May 31;6:26568.

A Novel Complotype Combination Associates with Age-Related Macular Degeneration and High Complement Activation Levels in vivo.

Paun CC, Lechanteur YT, Groenewoud JM, Altay L, Schick T, Daha MR, Fauser S, Hoyng CB, den Hollander AI, de Jong EK.

Abstract: The complement system is the first line of defense against foreign intruders, and deregulation of this system has been described in multiple diseases. In age-related macular degeneration (AMD), patients have higher complement activation levels compared to controls. Recently, a combination of three single nucleotide polymorphisms (SNPs) in genes of the complement system, referred to as a complotype, has been described to increase complement activation in vitro. Here we describe a novel complotype composed of CFB (rs4151667)-CFB (rs641153)-CFH (rs800292), which is strongly associated with both AMD disease status (p = 5.84*10(-13)) and complement activation levels in vivo (p = 8.31*10(-9)). The most frequent genotype combination of this complotype was associated with the highest complement activation levels in both patients and controls. These findings are relevant in the context of complement-lowering treatments for AMD that are currently under development. Patients with a genetic predisposition to higher complement activation levels will potentially benefit the most of such treatments.

PMID: 27241480 [PubMed - in process]

PLoS One. 2016 Jun 3;11(6):e0157210.

Correction: High-Density Lipoprotein Function in Exudative Age-Related Macular Degeneration.

Pertl L, Kern S, Weger M, Hausberger S, Trieb M, Gasser-Steiner V, Haas A, Scharnagl H, Heinemann A, Marsche G.

[This corrects the article DOI: 10.1371/journal.pone.0154397.].

PMID: 27258027 [PubMed - as supplied by publisher]

Genetics

J Curr Ophthalmol. 2016 Mar 8;28(1):32-6. eCollection 2016.

Complement factor H and LOC387715/ARMS2/HTRA1 variant's frequencies and phenotypic associations in neovascular age-related macular degeneration, a pilot study.

Karkhane R, Ahmadraji A, Riazi Esfahani M, Roohipour R, Alami Harandi Z, Lashay A, Kermani MS, Roozafzoon R, Khoshzaban A.

PURPOSE: To evaluate the frequency of 12 single nucleotide polymorphisms (SNPs) of complement factor H (CFH) and LOC387715/ARMS2/HRTA1 and their association with some of the presenting clinical features of neovascular age-related macular degeneration (AMD).

METHODS: In this prospective non-comparative case series forty four naïve patients with neovascular AMD were genotyped using sequencing or Sequenom iPLEX technology. Descriptive tests were used for displaying the magnitude of each allele, gender distribution, and age at diagnosis. Fisher exact test was used to evaluate the correlation between visual acuity (VA) and different alleles. Also Kruskal-Wallis test was used for comparison between age at the time of diagnosis and different alleles.

RESULTS: The most frequent SNP among studied patients was rs1061147 with 100% frequency rate. The least common was rs2672598 with a frequency of 52.27%. Only the allele rs800292 of CFH locus on 1q32 was associated with VA better than 20/200 (p value = 0.034). The frequency of this allele was 77.27% (34 patients) in this study. There was no significant association between any of alleles, and VA worse than 20/200(p > 0.05). Fifteen patients had bilateral exudative AMD (34.09%). There was no significant difference between alleles in bilateral neovascular AMD and unilateral disease. Also bilateral and unilateral patients were not different in terms of age, gender or VA (p value: 0.330, 0.764 and 0.456 respectively). There was also no significant association between any of SNPs and bilaterality of disease.

CONCLUSION: We designated the frequencies of SNPs of CFH and LOC387715/ARMS2/HRTA1 in neovascular AMD in a sample of Iranian patients. Only the allele rs800292 of CFH locus on chromosome 1q32 was associated with better VA.

PMID: 27239600 [PubMed] PMCID: PMC4881216

PLoS One. 2016 Jun 3;11(6):e0156778.

Genetics of Unilateral and Bilateral Age-Related Macular Degeneration Severity Stages.

Schick T, Altay L, Viehweger E, Hoyng CB, den Hollander AI, Felsch M, Fauser S.

BACKGROUND: Age-related macular degeneration (AMD) is a common disease causing visual impairment and blindness. Various gene variants are strongly associated with late stage AMD, but little is known about the genetics of early forms of the disease. This study evaluated associations of genetic factors and different AMD stages depending on unilateral and bilateral disease severity.

METHODS: In this case-control study, participants were assigned to nine AMD severity stages based on the characteristics of each eye. 18 single nucleotide polymorphisms (SNPs) were genotyped and attempted to correlate with AMD severity stages by uni- and multivariate logistic regression analyses and trend analyses. Area under the receiver operating characteristic curves (AUC) were calculated.

RESULTS: Of 3444 individuals 1673 were controls, 379 had early AMD, 333 had intermediate AMD and 989 showed late AMD stages. With increasing severity of disease and bilateralism more SNPs with significant associations were found. Odds ratios, especially for the main risk polymorphisms in ARMS2 (rs10490924) and CFH (rs1061170), gained with increasing disease severity and bilateralism (exemplarily: rs1061170: unilateral early AMD: OR = 1.18; bilateral early AMD: OR = 1.20; unilateral intermediate AMD: OR = 1.28; bilateral intermediate AMD: OR = 1.39, unilateral geographic atrophy (GA): OR = 1.50; bilateral GA: OR = 1.71). Trend analyses showed $p<0.0001$ for ARMS2 (rs10490924) and for CFH (rs1061170), respectively. AUC of risk models for various AMD severity stages was lowest for unilateral early AMD (AUC = 0.629) and showed higher values in more severely and bilaterally affected individuals being highest for late AMD with GA in one eye and neovascular AMD in the other eye (AUC = 0.957).

CONCLUSION: The association of known genetic risk factors with AMD became stronger with increasing disease severity, which also led to an increasing discriminative ability of AMD cases and controls. Genetic predisposition was also associated with the disease severity of the fellow-eye, highlighting the importance of both eyes in AMD patients.

PMID: 27257685 [PubMed - as supplied by publisher]

Sci Rep. 2016 May 31;6:26885.

Assessment of polygenic effects links primary open-angle glaucoma and age-related macular degeneration.

Cuellar-Partida G, Craig JE, Burdon KP, Wang JJ, Vote BJ, Souzeau E, McAllister IL, Isaacs T, Lake S, Mackey DA, Constable IJ, Mitchell P, Hewitt AW, MacGregor S.

Abstract: Primary open-angle glaucoma (POAG) and age-related macular degeneration (AMD) are leading causes of irreversible blindness. Several loci have been mapped using genome-wide association studies. Until very recently, there was no recognized overlap in the genetic contribution to AMD and POAG. At genome-wide significance level, only ABCA1 harbors associations to both diseases. Here, we investigated the genetic architecture of POAG and AMD using genome-wide array data. We estimated the heritability for POAG ($h(2)g = 0.42 \pm 0.09$) and AMD ($h(2)g = 0.71 \pm 0.08$). Removing known loci for POAG and AMD decreased the h(2)g estimates to 0.36 and 0.24, respectively. There was evidence for a positive genetic correlation between POAG and AMD ($rg = 0.47 \pm 0.25$) which remained after removing known loci ($rg = 0.64 \pm 0.31$). We also found that the genetic correlation between sexes for POAG was likely to be less than 1 (rg

= 0.33 ± 0.24), suggesting that differences of prevalence among genders may be partly due to heritable factors.

PMID: 27241461 [PubMed - in process]

PLoS One. 2016 Jun 3;11(6):e0144367.

Analysis of Risk Alleles and Complement Activation Levels in Familial and Non-Familial Age-Related Macular Degeneration.

Saksens NT, Lechanteur YT, Verbakel SK, Groenewoud JM, Daha MR, Schick T, Fauser S, Boon CJ, Hoyng CB, den Hollander AI.

AIMS: Age-related macular degeneration (AMD) is a multifactorial disease, in which complement-mediated inflammation plays a pivotal role. A positive family history is an important risk factor for developing AMD. Certain lifestyle factors are shown to be significantly associated with AMD in non-familial cases, but not in familial cases. This study aimed to investigate whether the contribution of common genetic variants and complement activation levels differs between familial and sporadic cases with AMD.

METHODS AND RESULTS: 1216 AMD patients (281 familial and 935 sporadic) and 1043 controls (143 unaffected members with a family history of AMD and 900 unrelated controls without a family history of AMD) were included in this study. Ophthalmic examinations were performed, and lifestyle and family history were documented with a questionnaire. Nine single nucleotide polymorphisms (SNPs) known to be associated with AMD were genotyped, and serum concentrations of complement components C3 and C3d were measured. Associations were assessed in familial and sporadic individuals. The association with risk alleles of the age-related maculopathy susceptibility 2 (ARMS2) gene was significantly stronger in sporadic AMD patients compared to familial cases ($p = 0.017$ for all AMD stages and $p = 0.003$ for advanced AMD, respectively). ARMS2 risk alleles had the largest effect in sporadic cases but were not significantly associated with AMD in densely affected families. The C3d/C3 ratio was a significant risk factor for AMD in sporadic cases and may also be associated with familial cases. In patients with a densely affected family this effect was particularly strong with ORs of 5.37 and 4.99 for all AMD and advanced AMD respectively.

CONCLUSION: This study suggests that in familial AMD patients, the common genetic risk variant in ARMS2 is less important compared to sporadic AMD. In contrast, factors leading to increased complement activation appear to play a larger role in patients with a positive family history compared to sporadic patients. A better understanding of the different contributions of risk factors in familial compared to non-familial AMD will aid the development of reliable prediction models for AMD, and may provide individuals with more accurate information regarding their individual risk for AMD. This information is especially important for individuals who have a positive family history for AMD.

PMID: 27258093 [PubMed - as supplied by publisher]

Front Aging Neurosci. 2016 May 23;8:115. eCollection 2016.

AMD Genetics in India: The Missing Links.

Anand A, Sharma K, Sharma SK, Singh R, Sharma NK, Prasad K.

Abstract: Age related macular degeneration is a disease which occurs in aged individuals. There are various changes that occur at the cellular, molecular and physiological level with advancing age (Samiec et al., 1988; Sharma K. et al., 2014). Drusen deposition between retinal pigment epithelium (RPE) and Bruch's membrane (BM) is one of the key features in AMD patients (Mullins et al., 2000; Hageman et al., 2001) similar to Aβ/tau aggregates in Alzheimer's disease (AD) patients. The primary goal of this review is to discuss whether the various candidate genes and associated biomarkers, that are known to play an independent role in progression of AMD, exert deleterious effect on phenotype, alone or in combination, in Indian AMD patients from the same ethnic group and the significance of such research. A statistical model for probable interaction between genes could be derived from such analysis. Therefore, one can use

multiple modalities to identify and enrol AMD patients based on established clinical criteria and examine the risk factors to determine if these genes are associated with risk factors, biomarkers or disease by Mendelian randomization. Similarly, there are large numbers of single nucleotide polymorphisms (SNPs) identified in human population. Even non-synonymous SNPs (nsSNPs) are believed to induce deleterious effects on the functionality of various proteins. The study of such snSNPs could provide a better genetic insight for diverse phenotypes of AMD patients, predicting significant risk factors for the disease in Indian population. Therefore, the prediction of biological effect of nsSNPs in the candidate genes and the associated grant applications in the subject are highly solicited.Therefore, genotyping and levels of protein expression of various genes would provide wider canvas in genetic complexity of AMD pathology which should be evaluated by valid statistical and bioinformatics' tools. Longitudinal follow up of Indian AMD patients to evaluate the temporal effect of SNPs and biomarkers on progression of disease would provide a unique strategy in the field.

PMID: 27252648 [PubMed]

Stem cells

Curr Eye Res. 2016 Jun 3:1-11. [Epub ahead of print]

Impact of Storage Temperature on the Expression of Cell Survival Genes in Cultured ARPE-19 Cells.

Pasovic L, Eidet JR, Olstad OK, Chen DF, Lyberg T, Utheim TP.

PURPOSE: The development of a suitable storage method for retinal pigment epithelium (RPE) is necessary in the establishment of future RPE replacement therapy, and storage temperature has proven to be pivotal for cell survival. ARPE-19, a widely used model for RPE, has been shown to yield the greatest number of viable cells when stored at 16°C compared to other storage temperatures. In this study, we analyze the gene expression profile of cultured ARPE-19 cells after seven days of storage at different temperatures in an effort to predict the gene-level consequences of storage of RPE transplants.

MATERIALS AND METHODS: ARPE-19 cells were cultured until confluence and then stored in minimum essential medium at 4°C, 16°C, and 37°C for seven days. The total RNA was isolated and the gene expression profile was determined using DNA microarrays. The Results were validated using qPCR.

RESULTS: Principal component and hierarchical clustering analyses show that the gene expression profiles of cell cultures stored at different temperatures cluster into separate groups. Cultures stored at 4°C cluster closest to the control cultures that were not stored and display the least change in gene expression after storage (157 differentially expressed genes). Cultures stored at 16°C and 37°C display a much larger change in differential gene expression (1787 and 1357 differentially expressed genes, respectively). At 16° C, the expression of several genes with proposed tumor suppressor functions was markedly increased. Changes in regulation of several known signaling pathways and of oxidative stress markers were discovered at both 16°C and 37°C, and activation of the angiogenesis marker vascular endothelial growth factor (VEGF) was discovered at 37°C. There was no evidence of the activation of inflammatory processes in stored cell cultures.

CONCLUSION: ARPE-19 cultures stored at 16°C show the greatest propensity to modulate their gene expression profile in a manner that supports cell survival during storage.

PMID: 27259952 [PubMed - as supplied by publisher]

Diet, lifestyle & low vision

Patient. 2016 Jun 2. [Epub ahead of print]

How Well Can Analytic Hierarchy Process be Used to Elicit Individual Preferences? Insights from a Survey in Patients Suffering from Age-Related Macular Degeneration.

Danner M, Vennedey V, Hiligsmann M, Fauser S, Gross C, Stock S.

BACKGROUND: In this study, we tested the feasibility of an interviewer-assisted analytic hierarchy process (AHP) in a special patient population with age-related macular degeneration (AMD).

OBJECTIVES: One aim was to generate preference weights regarding AMD treatment characteristics. A secondary aim was to explore the consistency of preference judgments and reasons for inconsistency.

METHODS: We generated quantitative importance weights for decision criteria using the matrix multiplication method. A qualitative study component in the form of asking patients to think aloud throughout their judgments was implemented to facilitate understanding of quantitative findings. Consistency ratios were calculated as a measure of logical judgment performance within AHP. If consistency ratios exceeded 0.2, we explored reasons for inconsistency.

RESULTS: We interviewed 86 patients and generated preference weights for criteria. Patients rated the injection's effect on visual function the highest (0.44), followed by the frequency of monitoring visits (0.18), approval status (0.13), injection frequency (0.13), and side effects (0.12). Inconsistency in judgments was prevalent at the subcriteria level. Whereas much of the observed inconsistency was due to an excessive use of high/extreme value judgments, these judgments seemed to result from patients reasonably trying to highlight their strong preferences.

CONCLUSION: Our study combines quantitative with qualitative data to explore patients' preference weights and decision processes using the AHP. It suggests that the type of inconsistency observed in judgments of AMD patients mostly results from rational decision making, not from error or lack of understanding. Further research should address which type and extent of inconsistency might be acceptable in different AHP settings.

PMID: 27255773 [PubMed - as supplied by publisher]