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Drug treatment

Retina. 2012 Mar 12. [Epub ahead of print]

RETREATMENT WITH ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY BASED ON CHANGES IN VISUAL ACUITY AFTER INITIAL STABILIZATION OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: 3-Year Follow-up Results.

Dunavoelgyi R, Sacu S, Eibenberger K, Palkovits S, Leydolt C, Pruente C, Schmidt-Erfurth U.

Department of Ophthalmology, Medical University of Vienna, Austria.

PURPOSE: To evaluate the 3-year therapeutic benefit of intravitreal bevacizumab in neovascular related macular degeneration (nAMD) in a standard clinical setting involving 3 initial injections and a pro re nata regimen as recommended in the PRONTO study.

METHODS: In this interventional clinical study, 181 eyes of 160 consecutive patients with active neovascular related macular degeneration meeting recommended criteria for inclusion and protocol criteria for anti-vascular endothelial growth factor therapy undergoing intravitreal bevacizumab monotherapy were observed. Data of treatment-naive eyes (Group 1, n = 114) were analyzed separately from eyes that had undergone previous photodynamic therapy plus intravitreal triamcinolone (Group 2, n = 67). Re-treatment criteria were based on clinical outcome following the official European label regimen. After 1 year of continuous service at an academic referral center, follow-up was performed in private practices in collaboration with the referral center. Main outcome parameters were best-corrected visual acuity and central retinal thickness.

RESULTS: After 3 years, best-corrected visual acuity decreased in the overall population (0.23 ± 0.16 to 0.16 ± 0.21. P = 0.002) and in both groups compared with baseline (0.24 ± 0.21 to 0.17 ± 0.21, Group 1, P = 0.03; 0.22 ± 0.19 to 0.16 ± 0.21, Group 2, P > 0.05), whereas central retinal thickness increased in the overall population (291 ± 92 to 319 ± 110 μm, P = 0.01) and in both groups (291 ± 96 to 325 ± 117 μm, Group 1, P > 0.05; 290 ± 83 to 308 ± 96 μm, Group 2, P > 0.05) because of chronic cystic degeneration changes of the macula. Mean treatment rate was 5.1 ± 3.9 (Group 1) versus 3.7 ± 2.7 (Group 2, P = 0.01). Five cases of severe intraocular inflammation after intravitreal bevacizumab were documented.

DISCUSSION: While the functional and morphological benefits persisted for the first year after intravitreal bevacizumab treatment, after this time both functional and morphologic results were disappointing during long-term follow-up with visual acuity loss as the main retreatment criterion. After stabilization of the disease, a monthly follow-up of optical coherence tomography and re-treatment based on morphologic, clinical, and vision outcomes may increase the efficacy in patients with neovascular related macular degeneration under anti-vascular endothelial growth factor treatment.

PMID: 22414958 [PubMed - as supplied by publisher]

Cochrane Database Syst Rev. 2012 Mar 14;3:CD006927.

Statins for age-related macular degeneration.

Gehlbach P, Li T, Hatef E.

Retina Division, Wilmer Eye Institute, Johns Hopkins University School of Medicine, 1550 Orleans Street, Cancer Research Building #2, Baltimore, Maryland, USA, 21231.

BACKGROUND: Age-related macular degeneration (AMD) is a progressive late onset disorder of the macula affecting central vision. Age-related macular degeneration is the leading cause of blindness in people over 65 years in industrialized countries (Congdon 2003). Recent epidemiologic, genetic and pathological evidence has shown AMD shares a number of risk factors with atherosclerosis, leading to the hypothesis that statins may exert protective effects in AMD.

OBJECTIVES: To examine the effectiveness of statins compared with other treatments, no treatment, or placebo in delaying the onset and/or progression of AMD.

SEARCH METHODS: We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (The Cochrane Library 2011, Issue 9), MEDLINE (January 1950 to September 2011), EMBASE (January 1980 to September 2011), Latin American and Caribbean Health Sciences Literature Database (LILACS) (January 1982 to September 2011), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). There were no date or language restrictions in the electronic searches for trials. The electronic databases were last searched on 16 September 2011.

SELECTION CRITERIA: We included randomized controlled trials (RCTs) that compared statins with other treatments, no treatment, or placebo in participants who were either susceptible to or diagnosed as having early stages of AMD.

DATA COLLECTION AND ANALYSIS: Two authors independently evaluated the search results against the selection criteria. Two Italian speaking colleagues extracted data. One author entered data. We did not perform a meta-analysis because only one completed RCT was identified.

MAIN RESULTS: Two studies met the selection criteria. One trial reported insufficient details to assess the risk of bias; the other trial is ongoing.Of the completed trial, the analyses of 30 participants did not show a statistically significant difference between the simvastatin and the placebo arm in visual acuity at three months of treatment (decimal visual acuity 0.21± 0.56 in simvastatin and 0.19± 0.40 in placebo arm) or 45 days after the completion of treatment (decimal visual acuity 0.20± 0.50 in simvastatin and 0.19± 0.48 in placebo arm). The lens and retina status were unchanged during and after the treatment period for both groups.Of the ongoing trial, the preliminary analyses of 42 participants who completed 12 months follow-up did not show a statistically significant difference between the simvastatin and the placebo arm in visual acuity, drusen score or visual function (effect estimates and confidence intervals were not available). We contacted the investigators and will update the review as data become available.

AUTHORS' CONCLUSIONS: Evidence from currently available RCTs was insufficient to conclude that statins have any role in preventing or delaying the onset or progression of AMD.

PMID: 22419318 [PubMed - in process]

Ophthalmology. 2012 Mar 13. [Epub ahead of print]

Changes in Antibiotic Resistance Patterns of Conjunctival Flora Due to Repeated Use of Topical Antibiotics after Intravitreal Injection.

Milder E, Vander J, Shah C, Garg S.

OBJECTIVE: To determine the effect of repeated intermittent use of topical antibiotics after intravitreal injections on conjunctival bacterial flora and antibiotic resistance.

DESIGN: Cross-sectional case-control study.

PARTICIPANTS AND CONTROLS: A total of 80 eyes of 40 patients were enrolled (40 study eyes, 40 control eyes). Patients were enrolled with unilateral exudative age-related macular degeneration who had received at least 3 prior intravitreal injections with use of postinjection topical antibiotics. Patients had received an average of 7 (range, 3-13) intravitreal injections before enrollment.

METHODS: At the time of enrollment, the inferior fornix of the treated eye was swept with a culture swab before use of povidone iodine; the inferior fornix of the fellow eye was also cultured and served as a control. The culture and sensitivity data from the study and control eyes were analyzed.

MAIN OUTCOME MEASURES: The rate of antibiotic resistance among the conjunctival bacterial flora of the study eyes and control eyes.

RESULTS: A total of 80 eyes of 40 patients were enrolled in the study; 29 patients used trimethoprim/polymyxin B drops, and 11 patients used fluoroquinolone drops after each injection. A total of 58 bacterial colonies were isolated from 50 eyes. There were no significant differences in bacterial species or culture positivity rates between study and control eyes. Coagulase-negative staphylococcus accounted for 41 of the 58 bacterial colonies (71%). There was a 63.6% resistance rate to fluoroquinolones among study eyes, compared with 32.1% among control eyes ($P < 0.05$). In the subset of 11 study eyes using fluoroquinolone drops for 4 days after injection, there was an 87.5% resistance rate compared with 25.0% in matched control eyes ($P = 0.04$). There was no significant difference in trimethoprim resistance rates between study and control eyes: Four of 14 study eyes (28.6%) showed resistance compared with 5 of 18 control eyes (27.7%) ($P = 1.0$).

CONCLUSIONS: Use of fluoroquinolone drops after intravitreal injection leads to increased rates of resistance among conjunctival flora. Repeated use of topical fluoroquinolones after intravitreal injections may have a detrimental effect on eye health by breeding resistance in the bacterial flora.

PMID: 22420958 [PubMed - as supplied by publisher]

Scott Med J. 2012 Feb;57(1):48-9.

The importance of informed consent in patients with wet age-related macular degeneration considering intravitreal anti-vascular endothelial growth factor treatments.

McLaughlin S, Lockington D, Mansfield D.

Tennent Institute of Ophthalmology, Gartnavel General Hospital, Glasgow G12 0YN, Scotland, UK.

Abstract

Retinal pigment epithelial (RPE) tears are now a documented potential complication following the intravitreal injection of anti-vascular endothelial growth factor (VEGF) treatments for neovascular age-related macular degeneration. Patients are often not well consented regarding this risk and thus we retrospectively analyzed the data from all of our patients undergoing this treatment over a six month period. Our findings highlighted the fact that the three patients (out of thirty) who had developed this RPE tear complication were initially all diagnosed with a pigment epithelial detachment (which is a type of macular degeneration in question). Therefore, we have adjusted our informed consent procedure such that all patients with "wet" macular degeneration and especially those with pigment epithelial detachments are now fully consented regarding the risks of the intravitreal treatment, which could potentially damage their vision further.

PMID: 22408217 [PubMed - in process]

Clin Ophthalmol. 2012;6:365-8. Epub 2012 Mar 6.

Comparison of the effect between pegaptanib and ranibizumab on exudative age-related macular degeneration with small lesion size.

Nishimura Y, Taguchi M, Nagai T, Fujihara M, Honda S, Uenishi M.

Department of Ophthalmology, Mitsubishi Kobe Hospital, Kobe, Japan.

PURPOSE: To compare the effect of pegaptanib versus ranibizumab on exudative age-related macular degeneration (AMD) with small lesion size.

METHODS: This is a retrospective study of 81 eyes from 78 patients with exudative AMD treated and followed up over 12 months. Patients with baseline best corrected visual acuity (BCVA) under 20/400 and with a greatest linear dimension of lesion over 4500 μm were excluded from the study. Twenty-six eyes from 25 patients were treated with three consecutive intravitreal injections of pegaptanib (IVP group) and 55 eyes from 54 patients were treated with three consecutive ranibizumab injections (IVR group). Each therapy was repeated as needed. The alteration in BCVA was evaluated in the IVP and IVR groups.

RESULTS: No differences were detected in baseline parameters between the IVP and IVR groups. The mean BCVA (logMAR) at month 1, 3, 6 and 12 after the initial treatment was improved from baseline in the IVP group (-0.095, -0.17, -0.18 and -0.18, respectively) and in the IVR group (-0.077, -0.15, -0.17 and -0.11, respectively), which was statistically significant. There was no difference in the change in mean BCVA between IVP and IVR groups at the same time periods.

CONCLUSIONS: The visual outcome of IVP was equivalent with IVR in exudative AMD with small lesion size.

PMID: 22419857 [PubMed - in process]

Other treatment & diagnosis

Invest Ophthalmol Vis Sci. 2012 Mar 12. [Epub ahead of print]

Peripheral Fundus Autofluorescence is Increased in Age-related Macular Degeneration.

Reznicek L, Wasfy T, Stumpf C, Kampik A, Ulbig M, Neubauer AS, Kernt M.

Augenklinik, Ludwig-Maximilians-University, Mathildenstr. 8, Munich, 80336, Germany.

Purpose: To evaluate peripheral fundus autofluorescence (FAF) in patients with age-related macular degeneration (AMD)

Methods: A consecutive series of 71 normal eyes, 71 eyes with neovascular AMD having received anti-VEGF treatment and 43 eyes with untreated AMD were investigated. In all subjects, wide-field FAF imaging was performed applying a wide-field scanning laser ophthalmoscope (Optomap® Panoramic 200Tx, Optos, Dunfermline, Scotland). FAF was quantified by image analysis software after defining peripheral and perifoveal central measurement zones with a grid scheme, age correction was performed by regression model.

Results: Fundus autofluorescence increased with age not only in the perifoveal retinal area, but also in the retinal periphery. For age corrected measurements peripheral FAF was significantly increased for both, treated and untreated AMD groups compared to normal subjects. No significant difference was observed in peripheral FAF between AMD eyes having received anti-VEGF treatment and those without treatment. Age corrected normal FAF in the retinal center differed significantly from the anti-VEGF treated group ($p<0.01$), but not the untreated AMD group. Age corrected peripheral FAF irregularity, defined as the standard deviation in the measurement field, was significantly increased in both AMD groups compared to normal subjects.

Conclusions: Detection of peripheral in addition to central FAF may provide additional information potentially helpful to detect and monitor the development of AMD. No differences in autofluorescence were observed in the retinal periphery between anti-VEGF treated and untreated eyes.

PMID: 22410571 [PubMed - as supplied by publisher]

Optom Vis Sci. 2012 Mar 7. [Epub ahead of print]

Scene Perception in Age-Related Macular Degeneration: The Effect of Contrast.

Tran TH, Despretz P, Boucart M.

Laboratoire de Neurosciences et Pathologies Fonctionnelles, CNRS, Université Lille Nord de France, Lille, France (THCT, PD, MB), and Service d'Ophtalmologie, Hôpital Saint Vincent de Paul, Université Catholique de Lille, Lille, France (THCT).

PURPOSE: To investigate the effect of contrast on scene perception in people with age-related macular degeneration (AMD) and to examine the relationship between task performance and macular function.

METHODS: Nineteen patients with AMD and visual acuity below 20/50 were compared with 16 normally sighted, age-matched controls. Complete ophthalmologic examination (visual acuity, intraocular pressure measurement, and funduscopy) was performed in both patients and controls. In addition, Pelli-Robson contrast sensitivity, fluorescein angiography, and visual field size were assessed in the AMD study patients. The stimuli were photographs of natural scenes containing or lacking an animal (the target). For each scene, the contrast of the original photograph was divided by 2, 4, and 8 to yield versions with a residual contrast of 50, 25, and 12.5%, respectively. The four levels of contrast were presented randomly and participants were asked to press a key when they saw an animal.

RESULTS: AMD patients exhibited a larger drop in target detection performance with the decrease in contrast than controls. We found a correlation between visual acuity and performance when the contrast was reduced to 50, 25, and 12.5% of the original value but not in the normal contrast condition. There were no correlations between letter contrast sensitivity, visual field lesion size, and performance.

CONCLUSIONS: Our results suggest that optimal, stable contrast conditions would facilitate object recognition in everyday life for people with AMD.

PMID: 22407253 [PubMed - as supplied by publisher]

Cell Transplant. 2012 Mar 8. [Epub ahead of print]

Focused magnetic stem cell targeting to the retina using superparamagnetic iron oxide nanoparticles.

Yanai A, Häfeli UO, Metcalfe AL, Soema P, Addo L, Gregory-Evans CY, Po K, Shan X, Moritz OL, Gregory-Evans K.

Abstract

Developing new ways of delivering cells to diseased tissue will be a key factor in translating cell therapeutics research into clinical use. Magnetically targeting cells enables delivery of significant numbers of cells to key areas of specific organs. To demonstrate feasibility in neurological tissue, we targeted cells magnetically to the upper hemisphere of the rodent retina. Rat mesenchymal stem cells (MSCs) were magnetized using superparamagnetic iron oxide nanoparticles (SPIONs). In vitro studies suggested that magnetization with fluidMAG-D was well tolerated, that cells remained viable and they retained their differentiation capabilities. FluidMAG-D labeled MSCs were injected intravitreally or via the tail vein of the S334ter-4 transgenic rat model of retinal degeneration with or without placing a gold-plated neodymium

disc magnet within the orbit, but outside the eye. Retinal flatmount and cryosection imaging demonstrated that after intravitreal injection cells localized to the inner retina in a tightly confined area corresponding to the position of the orbital magnet. After intravenous injection, similar retinal localization was achieved and remarkably was associated with a tenfold increase in magnetic MSC delivery to the retina. Cryosections demonstrated that cells had migrated into both the inner and outer retina. Magnetic MSC treatment with orbital magnet also resulted in significantly higher retinal concentrations of anti-inflammatory molecules interleukin-10 and hepatocyte growth factor. This suggested that intravenous MSC therapy also resulted in significant therapeutic benefit in the dystrophic retina. With minimal risk of collateral damage, these results suggest that magnetic cell delivery is the best approach for controlled delivery of cells to the outer retina - the focus for disease in age-related macular degeneration and retinitis pigmentosa.

PMID: 22405427 [PubMed - as supplied by publisher]

J Pharm Pharmacol. 2012 Apr;64(4):482-9. doi: 10.1111/j.2042-7158.2011.01427.x. Epub 2011 Dec 30.

Reliable and effective oxygen-ozone therapy at a crossroads with ozonated saline infusion and ozone rectal insufflation.

Bocci V, Zanardi I, Borrelli E, Travagli V.

Dip. di Fisiologia Dip. Farmaco Chimico Tecnologico Dip. di Chirurgia e Bioingegneria, Università degli Studi di Siena, Siena, Italy.

Objectives: This review aims to highlight the advantages and safety of oxygen-ozone therapy (OOT) and to suggest ways to enhance its acceptance.

Key findings: The treatment of a herniated disk by injecting a gaseous oxygen-ozone mixture inside the nucleus pulposus is a great clinical success. However, the use of OOT lags for a number of reasons, including lack of standardization, the need for numerous treatments, lack of knowledge and even denial. Anecdotally, several million treatments by OOT have been performed worldwide indicating its usefulness, mainly in peripheral arterial diseases and age-related macular degeneration. The scepticism that accompanies the systemic use of ozone can only be overcome by demonstrating the validity of OOT in controlled and randomized clinical trials. Cheaper and quicker methods, such as ozonating physiological saline with successive infusion as well as ozone rectal insufflations, are becoming popular, however, such alternative procedures are erratic, unstable and liable to be toxic, with deleterious consequences, and are likely to discredit the beneficial use of ozone.

Summary: The approval of ozone in terms of both therapeutic efficacy and safety will depend on the results achieved by authoritative clinical trials.

PMID: 22420654 [PubMed - in process]

Adv Exp Med Biol. 2012;724:15-36.

Age-related macular degeneration.

Khandhadia S, Cherry J, Lotery AJ.

Department of Clinical Neurosciences, Southampton General Hospital, Southampton, UK.

Abstract

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the developed world. Despite recent advances in treatment, AMD causes considerable morbidity. For the non-ophthalmologist, a brief background on retinal structure is provided, followed by a description of the characteristic changes seen in AMD. Subsequently the typical clinical features of AMD are discussed with

an outline of present management, followed by the current theories of AMD pathogenesis. The similarities between AMD and another neurodegenerative disease are then highlighted. Finally, we review the on-going clinical trials of potential treatments for the future. Since it is clear that multiple risk factors are involved in the pathogenesis of AMD, a multi-faceted approach will most likely be required in order to prevent further patients progressing to blindness as a result of this devastating condition.

PMID: 22411231 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2012 Mar 9;53(3):1276. Print 2012.

Validation of the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) in Age-Related Macular Degeneration.

Khadka J, McAlinden C, Pesudovs K.

National Health and Medical Research Council (NH&MRC) Centre for Clinical Eye Research, Discipline of Optometry and Vision Science, Flinders Medical Centre, Flinders University of South Australia, Bedford Park, South Australia.

PMID: 22408138 [PubMed - in process]

Pathogenesis

Mol Vis. 2012;18:574-80. Epub 2012 Mar 2.

Inflammatory cytokines in aqueous humor of patients with choroidal neovascularization.

Miao H, Tao Y, Li XX.

OBJECTIVE: To investigate the correlations between aqueous concentrations of interleukin 1β, 6, 8, 10, 12p (IL-1β, IL-6, IL-8, IL-10, IL-12p), and tumor necrosis factor α (TNF-α) and the parameters of macular edema acquired by optical coherence tomography (OCT) in patients with choroidal neovascularization.

METHODS: IL-1β, IL-6, IL-8, IL-10, IL-12p, and TNF-α in the aqueous humor samples of 17 patients with exudative age-related macular degeneration (AMD), ten patients with pathological myopia (PM), seven patients with idiopathic choroidal neovascularization (CNV), and 14 patients with cataract and idiopathic epiretinal membrane or macular hole in the control group were measured with cytometric bead array. The maximum macular thickness and macular volume within 1 mm, 3 mm, and 6 mm were measured with OCT.

RESULTS: In the CNV groups, the aqueous levels of IL-6 and IL-8 were significantly associated with macular volume within 6 mm (p=0.011, p=0.008, respectively), while IL-1β, IL-10, IL-12p, and TNF-α showed no significant correlation with either the maximum macular thickness or the macular volume. By further selecting patients with CNV who had accepted their last intravitreal injection of bevacizumab within 3 months, the level of IL-6 still significantly correlated with the maximum macular thickness (p=0.019) and macular volume within 1 mm (p=0.018), 3 mm (p=0.018), and 6 mm (p=0.022). In patients with exudative AMD, the level of IL-6 was significantly associated with the maximum macular thickness (p=0.025) and macular volume within 1 mm (p=0.025), 3 mm (p=0.006), and 6 mm (p=0.002). The aqueous level of all cytokines did not vary significantly between the CNV patients who had accepted their last intravitreal injection of bevacizumab within 3 months and the other patients, nor was a difference found among patients with exudative AMD, PM, and idiopathic CNV, and the control group.

CONCLUSIONS: Intraocular concentrations of IL-6 and IL-8 (particularly IL-6) are significantly associated with the volume of macular edema in patients with CNV. However, intravitreal injection of antivascular endothelial growth factor drugs did not change the intraocular level of these inflammation cytokines.

PMID: 22419849 [PubMed - in process]

Chem Biol Drug Des. 2012 Mar 8. doi: 10.1111/j.1747-0285.2012.01376.x. [Epub ahead of print]

Structure-Activity Relationship Study of Collagen derived Anti-Angiogenic Biomimetic Peptides.

Rosca EV, Koskimaki JE, Pandey NB, Tamiz AP, Popel AS.

Department of Biomedical Engineering, School of Medicine, Johns Hopkins University, Baltimore, MD 21205 Department of Oncology and the Sidney Kimmel Comprehensive Cancer Center, School of Medicine, Johns Hopkins University, Baltimore, MD 21231.

Abstract

Structure-activity relationship (SAR) studies are essential in the generation of peptides with enhanced activity and efficacy as therapeutic agents. In this study we report a SAR study for a family of mimetic peptides derived from type IV collagen with potent anti-angiogenic properties. The SAR study was conducted using a number of validated in vitro assays including cell proliferation, adhesion, migration and tubule formation. We report a critical sequence (NINNV) within this peptide series which is required for the potent anti-angiogenic activity. Detailed amino acid substitutions resulted in peptides with superior efficacy. Specifically, substitutions with Isoleucine at positions twelve and eighteen along with the substitution of the Methionine at position ten with the non-natural amino acid d-Alanine led to an increase in potency by two orders of magnitude over the parent peptide. Several mimetic peptides in this series exhibit a significant improvement of activity over the parent peptide. This improved in vitro activity is expected to correlate with an increase in in vivo activity leading to effective peptides for anti-angiogenic therapy for different disease applications including cancer and age-related macular degeneration.

PMID: 22405100 [PubMed - as supplied by publisher]

Mol Vis. 2012;18:519-27. Epub 2012 Mar 1.

Molecular regulation of vascular endothelial growth factor expression in the retinal pigment epithelium.

Ford KM, D'Amore PA.

PURPOSE: Vascular endothelial growth factor (VEGF) plays an important role in homeostasis and diseases of the retinal pigment epithelium (RPE), choriocapillaris, and, most notably, age-related macular degeneration (AMD). Although much is known about VEGF regulation in pathologies, little is known about the control of VEGF expression under normal conditions. VEGF expression has been previously shown to be regulated in coordination with cell differentiation in the muscle and kidney. We therefore tested the hypothesis that VEGF in the adult RPE would similarly be regulated in conjunction with differentiation.

METHODS: A human retinal pigment epithelium cell line (ARPE-19), a line of immortalized human RPE cells, was used for all experiments. RPE cells were polarized in culture for 4 weeks on laminin-coated Transwells. Levels of VEGF mRNA and protein were determined with real-time PCR and enzyme-linked immunosorbent assay, respectively. VEGF-luciferase reporter constructs were used to identify regions of the VEGF promoter that control VEGF expression in the RPE. Microphthalmia-associated transcription factor (MITF)-Tfe transcription factors were blocked using either a pan MITF-Tfe dominant negative or specific small interfering RNA (siRNA).

RESULTS: VEGF mRNA and protein secretion increased over time in the RPE cells cultured on Transwells, with protein secretion occurring in a polarized fashion primarily toward the basolateral side. Overexpression of a dominant negative that targets the MITF-Tfe family resulted in a 50% reduction in VEGF expression. The role of the MITF-Tfe family in VEGF regulation in the RPE was corroborated in studies with the VEGF-luciferase reporter constructs, where deletion of the distal VEGF promoter region containing putative binding sites for the MITF-Tfe family resulted in a 50% reduction in VEGF promoter activity. siRNA knockdown of the MITF-Tfe family individually, and in combination, revealed that downregulation of Tfe3 resulted in reduced VEGF expression.

CONCLUSIONS: Our results indicate that Tfe3, in conjunction with other MITF-Tfe members, regulates VEGF expression in the RPE and are consistent with the hypothesis that VEGF expression in RPE cells is regulated as part of their differentiation.

PMID: 22419845 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2012 Mar 9. [Epub ahead of print]

Matrix Metalloproteinase Activity Creates Pro-Angiogenic Environment In Primary Human Retinal Pigment Epithelial Cells Exposed To Complement.

Bandyopadhyay M, Rohrer B.

Ophthalmology, Medical University of South Carolina, 167 Ashley Avenue, Charleston, South Carolina, 29403.

Purpose: Mechanistic studies have shown that inflammation, complement activation, extracellular matrix (ECM) turnover, growth factor imbalance, and oxidative stress are fundamental components of age-related macular degeneration (AMD). Matrix metalloproteinases (MMPs) mediate ECM turnover, but also process various bioactive molecules. Here we tested whether complement attack on RPE monolayers changes MMP secretion and activation, thereby altering the availability of growth factors in the extracellular space.

Methods: Human embryonic RPE monolayers with stable transepithelial resistance (TER) were established. Complement activation was induced with H(2)O(2) and normal human serum (NHS). MMP-2/9, VEGF and PEDF protein, and mRNA levels were analyzed by Western blotting, ELISA, and real-time PCR; activity of MMP-2/9 by gelatin zymography.

Results: Complement activation resulted in a loss of TER, which required transient membrane attack complex (MAC) formation, activation of the alternative pathway, and VEGF secretion and signaling. Despite the generation of reactive oxygen species, cellular integrity or intracellular ATP levels were unaffected. However, expression of MMP-2/9 and their protease activity was elevated. Inhibition of MMP-2/9 activity increased PEDF and decreased VEGF levels in the apical and basal supernatants, but had no effect on their expression levels. VEGF levels in the supernatant correlated with the level TER reduction.

Conclusions: These studies suggest that complement activation, by altering the expression and activation of MMPs, has the ability to generate a pro-angiogenic environment by altering the balance between VEGF and PEDF. Our findings link reported results that have been associated with AMD pathogenesis; oxidative stress; complement activation; VEGF/PEDF ratio; and MMP activity.

PMID: 22408008 [PubMed - as supplied by publisher]

Epidemiology

Arch Ophthalmol. 2012 Mar 12. [Epub ahead of print]

Visual Impairment, Age-Related Eye Diseases, and Cognitive Function: The Singapore Malay Eye Study.

Ong SY, Cheung CY, Li X, Lamoureux EL, Ikram MK, Ding J, Cheng CY, Haaland BA, Saw SM, Venketasubramanian N, Chen CP, Wong TY.

Singapore National Eye Centre (Ms Ong, Drs Cheung, Lamoureux, Ikram, Ding, Cheng, Saw, and Wong, and Mr Li), Duke-NUS Graduate Medical School (Ms Ong and Drs Cheung, Lamoureux, Ikram, Cheng, Haaland, and Wong), and Departments of Epidemiology and Public Health (Drs Ikram, Cheng, and Saw), Statistics and Applied Probability (Dr Haaland), and Pharmacology (Dr Chen), Division of Neurology, National University Hospital (Drs Ikram and Venketasubramanian), and Department of Ophthalmology,

Yong Loo Lin School of Medicine (Drs Cheung, Cheng, and Wong), National University of Singapore, Singapore; Centre for Eye Research Australia, University of Melbourne, Melbourne, Victoria, Australia (Drs Lamoureux and Wong); and Department of Ophthalmology, Erasmus Medical Center, Rotterdam, the Netherlands (Dr Ikram).

OBJECTIVE: To describe the associations of visual impairment and major age-related eye diseases with cognitive function in an older Asian population.

METHODS: A population-based, cross-sectional study of 1179 participants aged 60 to 80 years from the Singapore Malay Eye study was conducted. Visual acuity was measured using the logMAR vision chart. Cataract and age-related macular degeneration were graded using the Wisconsin Cataract Grading System and the Wisconsin Age-Related Maculopathy Grading System, respectively. Glaucoma was diagnosed using the International Society Geographical and Epidemiological Ophthalmology criteria. Diabetic retinopathy was graded using the modified Airlie House classification system. Cognitive dysfunction was defined as a locally validated Abbreviated Mental Test using education-based cutoff scores.

RESULTS: After adjusting for age, sex, education level, income, and type of housing, persons with visual impairment before refractive correction (odds ratio [OR] = 2.59; 95% CI, 1.89-3.56) or after refractive correction (OR = 1.96; 95% CI, 1.27-3.02) and those with visual impairment due to cataract (OR = 2.75; 95% CI, 1.35-5.63) were more likely to have cognitive dysfunction. Only moderate to severe diabetic retinopathy was independently associated with cognitive dysfunction (OR = 5.57; 95% CI, 1.56-19.91) after controlling for concurrent age-related eye diseases. No significant independent associations were observed between cataract, age-related macular degeneration, or glaucoma and cognitive dysfunction.

CONCLUSIONS: Older persons with visual impairment, particularly those with visual impairment due to cataract, were more likely to have cognitive dysfunction. Furthermore, among the major age-related eye diseases, only diabetic retinopathy was associated with cognitive dysfunction.

PMID: 22410630 [PubMed - as supplied by publisher]

Genetics

Invest Ophthalmol Vis Sci. 2012 Mar 12. [Epub ahead of print]

DNA Methylation is Associated with Altered Gene Expression in AMD.

Hunter A, Spechler P, Cwanger A, Song Y, Zhang Z, Ying GS, Hunter AK, Dezoeten E, Dunaief J.

F.M. Kirby Center for Molecular Ophthalmology, Scheie Eye Institute, University of Pennsylvania, 303 Stellar Chance Labs, 422 Curie Blvd, Philadelphia, Pennsylvania, 19104, United States.

PURPOSE: Age related macular degeneration (AMD) is the leading cause of blindness in the elderly. Evidence suggests oxidative stress plays a role in the disease. To assess the potential contribution of epigenetic regulation of antioxidant genes relevant to AMD pathogenesis, we evaluated DNA methylation, a tissue specific genetic modulation that affects gene expression.

METHODS: Using the Infinium HumanMethylation 27 Illumina platform, we performed DNA bisulfite sequencing to compare the methylation status in post mortem RPE/choroid between patients with AMD vs. age-matched controls. Gene expression was assessed with the Affymetrix Exon Array. TaqMan gene expression assays were used for relative quantification (RT-PCR) confirmation of the expression array

RESULTS: Glutathione S-Transferase isoform mu1 (GSTM1) and mu5 (GSTM5) promoter methylation was confirmed by CpG island bisulfite pyrosequencing. To assess protein levels and localization, we employed Western analysis, immunohistochemistry and immunofluorescence with murine and human samples. RESULTS The mRNA levels of GSTM1 and GSTM5 were significantly reduced in AMD vs. age matched controls in retina pigment epithelium (RPE)/choroid and neurosensory retina (NSR) which corresponded to hypermethylation of the GSTM1 promoter. mRNA and protein levels were decreased (RPE to a greater

extent than NSR) in AMD post-mortem samples, irrespective of age. Immunohistochemistry and immunofluorescence confirm the enzymes' presence in the NSR and RPE.

CONCLUSIONS: Comparison of DNA methylation together with mRNA levels revealed significant differences between AMD versus normal retinas. The evidence presented suggests that GSTM1 and GSTM5 undergo epigenetic repression in AMD RPE/choroid, which may increase susceptibility to oxidative stress in AMD retinas.

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Ocular phenotype of CORD5, an autosomal dominant retinal dystrophy associated with PITPNM3 p.Q626H mutation.

Reinis A, Golovleva I, Köhn L, Sandgren O.

Department of Clinical Sciences/Ophthalmology, University Hospital, Umeå, Sweden Department of Medical Biosciences/Medical and Clinical Genetics, University Hospital, Umeå, Sweden.

Purpose: To describe in detail the phenotype of CORD5 in two families segregating a mutation c.1878G>C (p.Q626H) in the PITPNM3 gene.

Methods: The study included 35 individuals from two different families of Swedish origin, all heterozygous for a PITPNM3 p.Q626H mutation. All participants underwent ophthalmological examination including kinetic perimetry, and in selected cases adaptometry, colour vision tests and optical coherence tomography (OCT). Electrophysiological studies were also performed. In some cases, the data were obtained from medical records.

Results: The majority of patients showed subnormal visual acuity and light sensitivity from childhood. Early signs of macular degeneration were also observed. There was a progressive decrease in visual acuity leading to legal blindness in early adulthood. Electrophysiological testing showed a progressive loss of photoreceptor function restricted mainly to the cones. OCT revealed decreased macular thickness with flattened and enlarged fovea.

Conclusion: Our observations of the PITPNM3 p.Q626H mutation carriers confirm that CORD5 is a disease not to mix with other retinal degenerations mapped to 17p13. The results of our clinical evaluation so far indicate that CORD5 is characterized by predominant cone dysfunction without signs of general involvement of the retinal pigment epithelium. The rod system also seems to be unaffected. In this sense, CORD5 is different from other autosomal dominant CORDs where rod involvement is present to some degree in a late phase of the disease. Some intra- and inter-familial differences regarding the severity of the clinical picture were observed.

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Diet

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Atmospheric Pressure Chemical Ionization Tandem Mass Spectrometry of Carotenoids.

van Breemen RB, Dong L, Pajkovic ND.

Department of Medicinal Chemistry and Pharmacognosy, University of Illinois College of Pharmacy, Chicago, IL 60612.

Abstract

Carotenoids are natural pigments synthesized by plants and photosynthetic microorganisms, some of which, like β-carotene, are precursors of vitamin A, and others such as lutein and lycopene might function in the prevention of age-related macular degeneration and prostate cancer, respectively. Mass spectrometry provides high sensitivity and selectivity for the identification and quantitative analysis of carotenoids in biological samples, and previous studies have described how atmospheric pressure chemical ionization (APCI) offers distinct advantages over electrospray and fast atom bombardment for the analysis of specific carotenoids. Since APCI product ion tandem mass spectra have been reported for only a few carotenoids, a detailed investigation of twelve carotenes and xanthophylls was carried out using both positive ion and negative ion APCI tandem mass spectrometry with collision-induced dissociation. Using protonated molecules as precursor ions in positive ion mode and radical anions in negative ion mode, characteristic fragment ions were identified that may be used to distinguish between carotenoids.

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