

Issue 93

Monday August 13, 2012

This free weekly bulletin lists the latest published research articles on macular degeneration (MD) as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases. These articles were identified by a search using the key term "macular degeneration".

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Drug treatment

PLoS One. 2012;7(8):e42701. Epub 2012 Aug 3.

A Safety Review and Meta-Analyses of Bevacizumab and Ranibizumab: Off-Label versus Goldstandard.

Schmucker C, Ehlken C, Agostini HT, Antes G, Ruecker G, Lelgemann M, Loke YK.

German Cochrane Institute, Institute of Medical Biometry and Medical Informatics, Department of Medical Biometry and Statistics, University Medical Centre Freiburg, Freiburg, Germany.

BACKGROUND: We set out a systemic review to evaluate whether off-label bevacizumab is as safe as licensed ranibizumab, and whether bevacizumab can be justifiably offered to patients as a treatment for age-related macular degeneration with robust evidence of no differential risk.

METHODS AND FINDINGS: Medline, Embase and the Cochrane Library were searched with no limitations of language and year of publication. We included RCTs with a minimum follow-up of one year which investigated bevacizumab or ranibizumab in direct comparison or against any other control group (indirect comparison). Direct comparison (3 trials, 1333 patients): The one year data show a significantly higher rate of ocular adverse effects (AE) with bevacizumab compared to ranibizumab (RR=2.8; 95% CI 1.2-6.5). The proportion of patients with serious infections and gastrointestinal disorders was also higher with bevacizumab than with ranibizumab (RR=1.3; 95% CI 1.0-1.7). Arterial thromboembolic events were equally distributed among the groups. Indirect comparison: Ranibizumab versus any control (5 trials, 4054 patients): The two year results of three landmark trials showed that while absolute rates of serious ocular AE were low ($\leq 2.1\%$), relative harm was significantly raised (RR=3.1; 95% CI 1.1-8.9). A significant increase in nonocular haemorrhage was also observed with ranibizumab (RR=1.7; 95% CI 1.1-2.7). Bevacizumab versus any control (3 trials, 244 patients): We were unable to judge the safety profile of bevacizumab due to the poor quality of AE monitoring and reporting in the trials.

CONCLUSIONS: Evidence from head-to-head trials raises concern about an increased risk of ocular and multiple systemic AE with bevacizumab. Therefore, clinicians and patients should continue to carefully weight up the benefits and harms when choosing between the two treatment options. We also emphasize the need for studies that are powered not just for efficacy, but for defined safety outcomes based on the signals detected in this systematic review.

PMID: 22880086 [PubMed - in process]

Expert Opin Biol Ther. 2012 Aug 7. [Epub ahead of print]

Systemic thromboembolic adverse events in patients treated with intravitreal anti-VEGF drugs for neovascular age-related macular degeneration.

Costagliola C, Agnifili L, Arcidiacono B, Duse S, Fasanella V, Mastropasqua R, Verolino M, Semeraro F.

Dipartimento di Scienze per la Salute, Cattedra di Oculistica , Università degli Studi del Molise , Campobasso , Italy.

Introduction: The consistent association between choroid neovascularization (CNV) and increased VEGF-A expression provides a strong reason for exploring the therapeutic potential of anti-VEGF agents in the treatment of neovascular age-related macular degeneration (AMD). The authors report the systemic side effects secondary to intravitreal administration of these compounds, that is, the main cardiovascular effects, as well as the less frequent cerebrovascular accidents, myocardial infarction, transient ischemic attacks, deep vein thrombosis, pulmonary embolism and thromboflebitis.

Areas covered: The authors reviewed major Clinical Trials and publications concerning systemic adverse events of anti-VEGF drugs in order to identify the main thromboembolic events related to the use of these agents and their occurrence. Anti-VEGF efficacy, safety and tolerability are also discussed.

Expert opinion: Three compounds (pegaptanib, ranibizumab and aflibercept) have been approved for the treatment of AMD; a fourth agent, bevacizumab, is used off-label. Anti-VEGF therapy has not shown the ability to fully eradicate the CNV, so that recurrences are common when the intravitreal injections are suspended. Although no evident rise in anti-VEGF-induced thromboembolic side effects was reported, more data are required to evaluate hemodynamic and pharmacokinetics of these compounds. Since only few studies have focused on these aspects, further researches are mandatory to determine distribution, effects and duration of these substances.

PMID: 22866908 [PubMed - as supplied by publisher]

Eye (Lond). 2012 Aug 10. doi: 10.1038/eye.2012.174. [Epub ahead of print]

Pilot study to evaluate the role of high-dose ranibizumab 2.0 mg in the management of neovascular age-related macular degeneration in patients with persistent/recurrent macular fluid <30 days following treatment with intravitreal anti-VEGF therapy (the LAST Study).

Fung AT, Kumar N, Vance SK, Slakter JS, Klancnik JM, Spaide RS, Freund KB.

Vitreous-Retina-Macula Consultants of New York and the LuEsther T. Mertz Retinal Research Center, Manhattan Eye, Ear and Throat Hospital, New York, NY, USA.

Purpose: To determine the efficacy of intravitreal ranibizumab 2.0 mg in patients with recalcitrant neovascular age-related macular degeneration (AMD).

Methods: This single-masked, randomized, prospective, pilot study enrolled patients with subfoveal neovascular AMD. All study eyes had persistent subretinal (SRF) or intraretinal fluid (IRF) on spectral-domain optical coherence tomography (SD-OCT) <30 days following at least 6 monthly intravitreal injections of ranibizumab or bevacizumab. Patients were randomized 2 : 1 to receive either ranibizumab 2.0 or 0.5 mg. Following three-loading treatments 4-weeks apart, both groups were treated using a 'treat and extend' regimen guided by eye-tracked SD-OCT through month 12. The primary end point was the mean change in best-corrected visual acuity (BCVA) at month 6.

Results: Nine eyes of 9 patients (mean age $\pm$ SD, 82.0 $\pm$ 5.8 years) were enrolled. Seven eyes received ranibizumab 2.0 mg and two eyes received 0.5 mg. Owing to the small number of patients enrolled, no statistical comparison could be made between the two dosages. At month 6, the mean improvement in BCVA was +6.1 $\pm$ 3.7 (W=0, P<0.001) ETDRS letters and +2.0 ETDRS letters in the 2.0 and 0.5 mg groups, respectively. In the 2.0 mg group, there was a statistically significant decline in central foveal thickness, SRF and maximum pigment epithelial detachment height at 6 months compared with baseline. No adverse events were reported in either group.

Conclusion: Ranibizumab 2.0 mg has the potential to maintain or improve BCVA in some patients with persistent or recurrent SRF or IRF secondary to neovascular AMD despite prior monthly intravitreal anti-vascular endothelial growth factor therapy with the standard dose. Eye advance online publication, 10 August 2012; doi:10.1038/eye.2012.174.

PMID: 22878451 [PubMed - as supplied by publisher]

BMC Ophthalmol. 2012 Aug 8;12(1):37. [Epub ahead of print]

A retrospective, pooled data analysis of the safety of pegaptanib sodium in the treatment of age-related macular degeneration in subjects with or without diabetes mellitus.

Dombi T, Kwok KK, Sultan MB.

BACKGROUND: To evaluate the safety of pegaptanib sodium 0.3 mg intravitreal injection in the treatment of neovascular age-related macular degeneration in subjects with or without diabetes mellitus.

METHODS: A pooled, retrospective, analysis was conducted of data from 9 sponsor-administered, randomized, open-label trials. Subjects who received pegaptanib by randomization or change in dose assignment, crossover design, or protocol amendment, were included. Reports of endophthalmitis, increased intraocular pressure, retinal injury, intraocular hemorrhage, traumatic cataract, hypersensitivity reactions, stroke, myocardial infarction, and other arterial thromboembolic events defined by the Antiplatelet Trialists' Collaboration were identified by Medical Dictionary for Regulatory Activities preferred terms. Adverse events were summarized from the first injection to 42 days after the last injection. The incidence of adverse events was stratified by the presence/absence of diabetes.

RESULTS: Of 1,586 subjects enrolled, 165 (10.4%) had a history of diabetes mellitus and 1,421 (89.6%) did not. The 2 populations were similar at baseline. Based on the comparison of prespecified ocular, hypersensitivity, and Antiplatelet Trialists' Collaboration event terms, the safety review did not identify any notable differences between the 2 populations.

CONCLUSIONS: This retrospective analysis found no increased safety risk resulting from treatment with pegaptanib 0.3 mg in individuals with neovascular age-related macular degeneration and concomitant diabetes mellitus.

PMID: 22871086 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2012 Aug 7. [Epub ahead of print]

Treating early choroidal neovascularisation with pegaptanib sodium in patients with neovascular age-related macular degeneration: Findings of the PERSPECTIVES study.

Chakravarthy U, Staurengi G, Kwok K, Tressler CS, Buggage R; For The PERSPECTIVES Study Group. Queens University of Belfast, Belfast, UK.

PMID: 22872673 [PubMed - as supplied by publisher]

Other treatment & diagnosis

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

Reproducibility of Activation Maps for Longitudinal Studies of Visual Function by Functional Magnetic Resonance Imaging.

Ming J, Thulborn KR, Szlyk JP.

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Purpose: To test the intra- and inter- subject reproducibility of brain activation patterns which underlie visually-guided saccades and word recognition in normally-sighted subjects and patients with macular degeneration using functional magnetic resonance imaging (fMRI).

Methods: Ten normally-sighted subjects and five patients with macular degeneration were asked to perform two visually-guided saccade tasks and two word recognition tasks during fMRI with behavioral monitoring. The fMRI measurements were repeated three times at intervals of at least four weeks between sessions. The intra-subject reproducibility of the brain activation patterns was examined in a model-independent manner by comparing the distributions of activation across the frontal, parietal, temporal and occipital brain lobes using Intra-class Correlation Coefficients (ICC). Inter-subject reproducibility was examined by repeated measure ANOVA.

Results: Control subjects showed overall higher intra-subject reproducibility of brain activation patterns (75% ICCs > 0.5) than patients with macular degeneration (56% ICCs > 0.5). The intra-subject reproducibility for the patients improved when the target location was fixed, as in the word recognition tasks (75% ICCs > 0.5), compared with the visually saccade tasks (37% ICCs > 0.5). Inter-subject variability of brain activation patterns was strikingly high for both the control and patient groups.

Conclusions: The fMRI method can serve as a reliable within-subjects measure of brain activation that has potential for measuring longitudinal changes in brain networks associated with rehabilitation training. Striking inter-subject variability reflected at the level of lobes of the brain among control subjects with similar behavioral performance, suggests individual analysis is necessary when implementing longitudinal brain activation studies.

PMID: 22879425 [PubMed - as supplied by publisher]

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

Image jitter enhances visual performance when spatial resolution is impaired.

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PURPOSE: Visibility of low spatial-frequency stimuli improves when their contrast is modulated at 5-10 Hz compared to stationary stimuli. Therefore, temporal modulations of visual objects could enhance the performance of low vision patients who primarily perceive images of low spatial-frequency content. We investigated the effect of retinal-image jitter on word recognition speed and facial emotion recognition in subjects with central visual impairment.

METHODS: Word recognition speed and accuracy of facial emotion discrimination were measured in volunteers with age-related macular degeneration under stationary and jittering conditions. Computer-driven and optoelectronic approaches were used to induce retinal-image jitter with duration of 100 or 166 ms and amplitude within the range of 0.5-2.6 deg. Word recognition speed was also measured for participants with simulated (Bangerter filters) visual impairment.

RESULTS: Text jittering markedly enhanced word recognition speed for people with severe visual loss ($101 \pm 25\%$), while for those with moderate visual impairment this effect was weaker ($19 \pm 9\%$). The ability of low vision patients to discriminate facial emotions of jittering images improved by a factor of 2. A prototype of optoelectronic jitter goggles produced similar improvement of facial emotion discrimination. Word recognition speed in participants with simulated visual impairment was enhanced for inter-jitter intervals over 100 ms and reduced for shorter intervals.

CONCLUSIONS: Results suggest that retinal-image jitter with optimal frequency and amplitude is an effective strategy for enhancing visual information processing in the absence of spatial detail. These findings will enable the development of novel tools to improve the quality of life of low vision patients.

PMID: 22879420 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2012 Aug 4. [Epub ahead of print]

Recombinant tissue plasminogen activator, vitrectomy, and gas for recent submacular hemorrhage displacement due to retinal macroaneurysm.

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BACKGROUND: The visual prognosis of submacular hemorrhages caused by a retinal arterial macroaneurysm (RAM) is poor if left untreated. The use of recombinant tissue plasminogen activator (rtPA) has frequently been reported to displace submacular hemorrhages from the foveal area in patients with age-related macular degeneration. This study aims to investigate the results of displacement of recent-onset submacular hemorrhages due to RAM.

METHODS: Institutional retrospective interventional case series of 12 patients with macular hemorrhage due to RAM, who underwent pars plana vitrectomy (PPV); followed in 11 by submacular injection of rtPA and gas tamponade. The main outcome measures were displacement of the hemorrhage, complication rate, and visual acuity at 1 month after surgery and at the last follow-up visit.

RESULTS: One month after surgery, the hemorrhage had been successfully displaced in ten out of 11 patients. In these ten patients, visual acuity (VA) increased by a mean of 1.2 logMAR at 1 month after surgery. At the last follow-up visit, the mean increase was 1.5 logMAR. Complications consisted of a vitreous hemorrhage and hyphema, retinal detachment, a new submacular hemorrhage, and vitreous hemorrhage after argon laser retinal photocoagulation of the RAM.

CONCLUSIONS: PPV with submacular rtPA and gas injection may successfully displace a recently developed submacular hemorrhage in patients with RAM, with a marked improvement in VA that is likely to be greater than if left untreated.

PMID: 22865261 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2012 Aug 3. [Epub ahead of print]

Detection of early-stage age related macular degeneration with a compact rarebit test.

de Kinkelder R, van Leeuwen TG, Verbraak FD.

Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.

PMID: 22863947 [PubMed - as supplied by publisher]

Optom Vis Sci. 2012 Aug 2. [Epub ahead of print]

Patient Awareness of Binocular Central Scotoma in Age-Related Macular Degeneration.

Fletcher DC, Schuchard RA, Renninger LW.

Department of Ophthalmology, California Pacific Medical Center, San Francisco, California (DCF), Smith-Kettlewell Eye Research Institute, San Francisco, California (DCF, LRW), and VAPAHCS Rehabilitation R&D, Stanford University School of Medicine, Palo Alto, California (RAS).

PURPOSE.: To assess whether age-related macular degeneration (AMD) patients are aware of binocular central visual field defects.

METHODS.: One hundred fifty-three consecutive AMD patients in their initial low-vision rehabilitation evaluation were immediately asked at the beginning of their visit (1) whether they were able to see any blind spots or defects in their field of vision and (2) whether they had any evidence or experiences that led them to believe that they had defects in their field of vision. They then had their vision assessed by binocular central visual field testing using the California Central Visual Field Test, binocular reading performance evaluated using the Smith-Kettlewell Reading Test (SK Read) and MN Read charts, and visual acuity measured using the ETDRS chart at 1 meter. Mean diameters of the scotomas with borders near fixation were noted.

RESULTS.: Visual acuity median was 20/253 (range 20/40 to hand movements). Binocular scotomas were present in 88% of patients (66% had dense scotoma). Of patients with binocular scotomas, 56% were totally unaware of their presence, even with dense scotomas measuring up to 30° in diameter; 1.5% could fleetingly see a defect in their visual field on waking; and 44% related experiences of things "disappearing" on them. The median and range of scotoma diameters for those unaware vs. those with some awareness of their scotomas were comparable. There was no significant relationship of awareness of the scotoma with age, acuity, scotoma size, density, or duration of onset. Awareness of scotoma was associated with fewer errors on the SK Read ($p < 0.01$).

CONCLUSIONS.: Low vision clinicians cannot depend on patients to report the presence of significant scotomas; thus, appropriate testing must be performed. Presence of scotomas decreased reading accuracy, but some awareness of the scotomas had a tendency to improve accuracy. The value of rehabilitation programs aimed at increasing patient awareness of their scotomas may be supported by this evidence.

PMID: 22863789 [PubMed - as supplied by publisher]

BMC Med Genet. 2012 Aug 3;13(1):67. [Epub ahead of print]

Molecular diagnosis of putative stargardt disease probands by exome sequencing.

Strom SP, Gao YQ, Martinez A, Ortube C, Chen Z, Nelson SF, Nusinowitz S, Farber DB, Gorin MB.

BACKGROUND: The commonest genetic form of juvenile or early adult onset macular degeneration is Stargardt Disease (STGD) caused by recessive mutations in the gene ABCA4. However, high phenotypic and allelic heterogeneity and a small but non-trivial amount of locus heterogeneity currently impede conclusive molecular diagnosis in a significant proportion of cases.

METHODS: We performed whole exome sequencing (WES) of nine putative Stargardt Disease probands and searched for potentially disease-causing genetic variants in previously identified retinal or macular dystrophy genes. Follow-up dideoxy sequencing was performed for confirmation and to screen for mutations in an additional set of affected individuals lacking a definitive molecular diagnosis.

RESULTS: Whole exome sequencing revealed seven likely disease-causing variants across four genes, providing a confident genetic diagnosis in six previously uncharacterized participants. We identified four previously missed mutations in ABCA4 across three individuals. Likely disease-causing mutations in RDS/PRPH2, ELOVL, and CRB1 were also identified.

CONCLUSIONS: Our findings highlight the enormous potential of whole exome sequencing in Stargardt Disease molecular diagnosis and research. WES adequately assayed all coding sequences and canonical splice sites of ABCA4 in this study. Additionally, WES enables the identification of disease-related alleles in other genes. This work highlights the importance of collecting parental genetic material for WES testing as the current knowledge of human genome variation limits the determination of causality between identified variants and disease. While larger sample sizes are required to establish the precision and accuracy of this type of testing, this study supports WES for inherited early onset macular degeneration disorders as an alternative to standard mutation screening techniques.

PMID: 22863181 [PubMed - as supplied by publisher]

Pathogenesis

Proc Natl Acad Sci U S A. 2012 Aug 6. [Epub ahead of print]

ERK1/2 activation is a therapeutic target in age-related macular degeneration.

Dridi S, Hirano Y, Tarallo V, Kim Y, Fowler BJ, Ambati BK, Bogdanovich S, Chiodo VA, Hauswirth WW, Kugel JF, Goodrich JA, Ponicsan SL, Hinton DR, Kleinman ME, Baffi JZ, Gelfand BD, Ambati J.

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Abstract

Deficient expression of the RNase III DICER1, which leads to the accumulation of cytotoxic Alu RNA, has been implicated in degeneration of the retinal pigmented epithelium (RPE) in geographic atrophy (GA), a late stage of age-related macular degeneration that causes blindness in millions of people worldwide. Here we show increased extracellular-signal-regulated kinase (ERK) 1/2 phosphorylation in the RPE of human eyes with GA and that RPE degeneration in mouse eyes and in human cell culture induced by DICER1 depletion or Alu RNA exposure is mediated via ERK1/2 signaling. Alu RNA overexpression or DICER1 knockdown increases ERK1/2 phosphorylation in the RPE in mice and in human cell culture. Alu RNA-induced RPE degeneration in mice is rescued by intravitreal administration of PD98059, an inhibitor of the ERK1/2-activating kinase MEK1, but not by inhibitors of other MAP kinases such as p38 or JNK. These findings reveal a previously unrecognized function of ERK1/2 in the pathogenesis of GA and provide a mechanistic basis for evaluation of ERK1/2 inhibition in treatment of this disease.

PMID: 22869729 [PubMed - as supplied by publisher]

PLoS One. 2012;7(8):e42542. Epub 2012 Aug 6.

MicroRNA-30b-Mediated Regulation of Catalase Expression in Human ARPE-19 Cells.

Haque R, Chun E, Howell JC, Sengupta T, Chen D, Kim H.

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BACKGROUND: Oxidative injury to retinal pigment epithelium (RPE) and retinal photoreceptors has been linked to a number of retinal diseases, including age-related macular degeneration (AMD). Reactive oxygen species (ROS)-mediated gene expression has been extensively studied at transcriptional levels. Also, the post-transcriptional control of gene expression at the level of translational regulation has been recently reported. However, the microRNA (miRNA/miR)-mediated post-transcriptional regulation in human RPE cells has not been thoroughly looked at. Increasing evidence points to a potential role of miRNAs in diverse physiological processes.

METHODOLOGY/PRINCIPAL FINDINGS: We demonstrated for the first time in a human retinal pigment epithelial cell line (ARPE-19) that the post-transcriptional control of gene expression via miRNA modulation regulates human catalase, an important and potent component of cell's antioxidant defensive network, which detoxifies hydrogen peroxide (H₂O₂) radicals. Exposure to several stress-inducing agents including H₂O₂ has been reported to alter miRNA expression profile. Here, we demonstrated that a sublethal dose of H₂O₂ (200 μM) up-regulated the expression of miR-30b, a member of the miR-30 family, which inhibited the expression of endogenous catalase both at the transcript and protein levels. However, antisense (antagomirs) of miR-30b was not only found to suppress the miR-30b mimics-mediated inhibitions, but also to dramatically increase the expression of catalase even under an oxidant environment.

CONCLUSIONS/SIGNIFICANCE: We propose that a microRNA antisense approach could enhance cytoprotective mechanisms against oxidative stress by increasing the antioxidant defense system.

PMID: 22880027 [PubMed - in process]

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

Pre-treatment with proteasome inhibitors protects against oxidative injuries via PPARα-dependent and independent pathways in ARPE-19 cells.

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Purposes: Oxidative processes may play important roles in age-related macular degeneration (AMD). Previous studies have suggested that enhancing proteasome activity by pre-treatment with low doses of proteasome inhibitors reduces injury from oxidative damage in neuronal cultures. The objective of the current study was to determine whether proteasome inhibitors could ameliorate the toxicity from oxidative stresses in ARPE-19 cells and to dissect the pathways that may mediate these protective effects.

Methods: The toxicity of oxidative stressors menadione (VK3) and 4-hydroxynonenal (4-HNE) and the protective effects of proteasome inhibitors, including MG-132 and clasto-lactacystinβ-lactone (LA) were studied in ARPE-19 cells. Binding and activation of the peroxisome proliferator-activated receptors (PPARs)

family of transcription factors were studied using electrophoretic mobility shift assay (EMSA) and a peroxisome proliferator-activated response element (PPRE)-driven dual-luciferase reporter gene. Results: 18 hr pre-treatment with 30-300 nM MG-132 or 300-1000 nM LA reduced the toxicity of menadione or 4-HNE in ARPE-19 cells. The protective effects of MG-132 pretreatment were partially reversed by the PPAR α antagonist GW6471 but not by the PPAR γ antagonist GW9662; in contrast, neither agent reduced the protective effects of LA. MG-132 but not LA induced increased expression of a PPRE-driven luciferase reporter gene in a dose-dependent manner. Nuclear proteins isolated from ARPE-19 cells treated by MG-132 had increased binding to PPRE sequences as measured by EMSA.

Conclusions: Our data suggests that pretreatment with proteasome inhibitors reduces oxidative injury in ARPE-19 cells and that the underlying mechanisms are different for different proteasome inhibitors, with PPAR α -dependent effects for MG-132 and PPAR-independent effects for LA.

PMID: 22879419 [PubMed - as supplied by publisher]

Int Rev Cell Mol Biol. 2012;298:135-77.

Mechanisms for countering oxidative stress and damage in retinal pigment epithelium.

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Abstract

Clinical and experimental evidence supports that chronic oxidative stress is a primary contributing factor to numerous retinal degenerative diseases, such as age-related macular degeneration (AMD). Eyes obtained postmortem from AMD patients have extensive free radical damage to the proteins, lipids, DNA, and mitochondria of their retinal pigment epithelial (RPE) cells. In addition, several mouse models of chronic oxidative stress develop many of the pathological hallmarks of AMD. However, the extent to which oxidative stress is an etiologic component versus its involvement in disease progression remains a major unanswered question. Further, whether the primary target of oxidative stress and damage is photoreceptors or RPE cells, or both, is still unclear. In this review, we discuss the major functions of RPE cells with an emphasis on the oxidative challenges these cells encounter and the endogenous antioxidant mechanisms employed to neutralize the deleterious effects that such stresses can elicit if left unchecked.

PMID: 22878106 [PubMed - in process]

FASEB J. 2012 Aug 7. [Epub ahead of print]

Translational attenuation differentially alters the fate of disease-associated fibulin proteins.

Hulleman JD, Balch WE, Kelly JW.

*Department of Chemistry.

Abstract

Mutations in fibulin proteins that cause cellular secretion deficiencies are linked to a variety of diseases, ranging from retinopathies to cutis laxa (CL). One secretion-deficient fibulin mutant, R345W fibulin-3, causes the macular dystrophy malattia leventinese by increased endoplasmic reticulum retention and/or

extracellular misfolding. Herein, we report that small-molecule activation of the PERK arm of the unfolded protein response partially rescues R345W secretion deficiencies through translational attenuation mediated by eIF2 α phosphorylation. Enhanced mutant fibulin-3 secretion can also be achieved by activation of a PERK-independent eIF2 α kinase through arsenite treatment and is independent of activating transcription factor 4 signaling and protein translation. However, this translational attenuation strategy was unsuccessful for enhancing the secretion deficiencies of fibulin-5 mutants associated with age-related macular degeneration or CL. While lowered growth temperature enhanced the secretion of mutants associated with CL (C217R and S227P), these effects were not mediated through translational attenuation. In stark contrast to the situation with fibulin-3, protein translation was required for efficient wild-type and mutant fibulin-5 secretion. These data suggest that alteration of specific cellular signaling pathways and proteostasis network components can differentially influence fibulin fate, a hypothesis that could be exploited as a therapy for fibulin-related diseases.-Hulleman, J. D., Balch, W. E., Kelly, J. W. Translational attenuation differentially alters the fate of disease-associated fibulin proteins.

PMID: 22872678 [PubMed - as supplied by publisher]

Ophthalmologica. 2012 Aug 4. [Epub ahead of print]

Vitreous Levels of Proteins Implicated in Angiogenesis Are Modulated in Patients with Retinal or Choroidal Neovascularization.

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Aim: The aim of this study was to investigate the levels of pigment epithelium-derived factor (PEDF), angiopoietin 2, vascular endothelial growth factor (VEGF), and soluble VEGF receptor 1 (sVEGFR-1) in vitreous samples of patients suffering from age-related macular degeneration with choroidal neovascularization or from proliferative diabetic retinopathy (PDR).

Methods: Proteins in vitreous samples of 29 patients were quantified via enzyme-linked immunosorbent assays.

Results: Vitreous levels of sVEGFR-1 were significantly higher in age-related macular degeneration with choroidal neovascularization ($p = 0.005$) and in PDR ($p = 0.003$) versus controls. In analogue comparisons, PEDF was significantly decreased ($p < 0.01$). PDR was associated with significantly increased angiopoietin 2 and VEGF levels ($p = 0.001$ for both).

Conclusion: The vitreous in retinal or choroidal neovascularization revealed a pro-angiogenic potential indicated by decreased PEDF or increased angiopoietin 2 levels compared to controls. However, higher amounts of sVEGFR-1 were concomitant, pointing to activation of an endogenous anti-angiogenic system in the protein network.

PMID: 22868384 [PubMed - as supplied by publisher]

Expert Opin Drug Discov. 2012 Aug 4. [Epub ahead of print]

Ocular disorders and the utility of animal models in the discovery of melatonineric drugs with therapeutic potential.

Crooke A, Huete-Toral F, Martínez-Águila A, Colligris B, Pintor J.

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Introduction: The pineal indole-derived hormone melatonin is a modulator of circadian and seasonal rhythms with an important role in ocular health and disease. This could be due to specific melatonin receptors that have been identified in structures such as cornea, lens, ciliary body, retina, choroid and sclera. In addition, a local synthesis of melatonin occurs in several of these ocular tissues.

Areas covered: The authors review existing literature on the most common animal models where ocular melatonin actions have been tested. The therapeutic potential of melatonin in diabetic keratopathy and retinopathy, keratitis, cataracts, glaucoma, uveitis, age-related macular degeneration and retinitis pigmentosa is discussed. Furthermore, the authors comment on the usefulness of different animal models for the development of melatonergic drugs with therapeutic potential.

Expert opinion: The use of animals for the study of ocular diseases and the potentiality of melatonin and its analogs, as future therapeutic drugs, should be performed on the basis of a rationale study. It is important to note that melatonin receptors seem to be widespread all over the eye. This strongly suggests that, in order to modify the physiology and biochemistry of malfunctioning ocular tissue, the melatonin receptors which are present in that tissue must be first identified. Second there is the need to confirm that those receptors targeted perform the desirable responses, and as a third measure, to use selective agonists (or antagonists) instead of melatonin. However, although some animals mimic ocular pathologies relatively well, and these can be used in melatonin studies, there is still a long way to go till some of the results obtained in animal models could be used for human therapy.

PMID: 22860991 [PubMed - as supplied by publisher]

Duke Med Health News. 2012 Jul;18(7):3.

Breakthrough in dry version of macular degeneration. Discovery of biological pathway may lead to cure for dry AMD.

[No authors listed]

PMID: 22872905 [PubMed - in process]

Genetics

Proc Natl Acad Sci U S A. 2012 Aug 8. [Epub ahead of print]

Complement factor H genotypes impact risk of age-related macular degeneration by interaction with oxidized phospholipids.

Shaw PX, Zhang L, Zhang M, Du H, Zhao L, Lee C, Grob S, Lim SL, Hughes G, Lee J, Bedell M, Nelson MH, Lu F, Krupa M, Luo J, Ouyang H, Tu Z, Su Z, Zhu J, Wei X, Feng Z, Duan Y, Yang Z, Ferreyra H, Bartsch DU, Kozak I, Zhang L, Lin F, Sun H, Feng H, Zhang K.

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Abstract

The rs1061170T/C variant encoding the Y402H change in complement factor H (CFH) has been identified by genome-wide association studies as being significantly associated with age-related macular

degeneration (AMD). However, the precise mechanism by which this CFH variant impacts the risk of AMD remains largely unknown. Oxidative stress plays an important role in many aging diseases, including cardiovascular disease and AMD. A large amount of oxidized phospholipids (oxPLs) are generated in the eye because of sunlight exposure and high oxygen content. OxPLs bind to the retinal pigment epithelium and macrophages and strongly activate downstream inflammatory cascades. We hypothesize that CFH may impact the risk of AMD by modulating oxidative stress. Here we demonstrate that CFH binds to oxPLs. The CFH 402Y variant of the protective rs1061170 genotype binds oxPLs with a higher affinity and exhibits a stronger inhibitory effect on the binding of oxPLs to retinal pigment epithelium and macrophages. In addition, plasma from non-AMD subjects with the protective genotype has a lower level of systemic oxidative stress measured by oxPLs per apolipoprotein B (oxPLs/apoB). We also show that oxPL stimulation increases expression of genes involved in macrophage infiltration, inflammation, and neovascularization in the eye. OxPLs colocalize with CFH in drusen in the human AMD eye. Subretinal injection of oxPLs induces choroidal neovascularization in mice. In addition, we show that the CFH risk allele confers higher complement activation and cell lysis activity. Together, these findings suggest that CFH influences AMD risk by modulating oxidative stress, inflammation, and abnormal angiogenesis.

PMID: 22875704 [PubMed - as supplied by publisher]

Am J Epidemiol. 2012 Aug 5. [Epub ahead of print]

The Association Between Complement Component 2/Complement Factor B Polymorphisms and Age-related Macular Degeneration: A HuGE Review and Meta-Analysis.

Thakkestant A, McEvoy M, Chakravarthy U, Chakrabarti S, McKay GJ, Ryu E, Silvestri G, Kaur I, Francis P, Iwata T, Akahori M, Arning A, Edwards AO, Seddon JM, Attia J.

Abstract

The authors performed a systematic review of the association of complement component 2(C2)/complement factor B (CFB) gene polymorphisms with age-related macular degeneration (AMD). In total, data from 19 studies published between 2006 and 2011 were pooled for 4 polymorphisms: rs9332739 and rs547154 in the C2 gene and rs4151667 and rs641153 in the CFB gene. Data extraction and assessments for risk of bias were independently performed by 2 reviewers. Allele frequencies and allele and genotypic effects were pooled. Heterogeneity and publication bias were explored. Pooled minor allele frequencies for all 4 SNPs were between 4.7% and 9.6% for all polymorphisms, except for an Indian population in which the C allele at rs9332739 was the major allele. For the C2 polymorphisms, the minor C allele at rs9332739 and the minor T allele at rs547154 carried estimated relative risks (odds ratios) of 0.55 (95% confidence interval (CI): 0.46, 0.65) and 0.47 (95% CI: 0.39, 0.57), respectively. For the CFB polymorphisms, the minor A alleles at rs4151667 and rs641153 carried estimated risks of 0.54 (95% CI: 0.45, 0.64) and 0.41 (95% CI: 0.34, 0.51), respectively. These allele effects contributed to an absolute lowering of the risk of all AMD in Caucasian populations by 2.0%-6.0%. This meta-analysis provides a robust estimate of the protective association of C2/CFB with AMD.

PMID: 22869612 [PubMed - as supplied by publisher]

Diet

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

Macular pigment imaging in AREDS2 participants: An ancillary study of AREDS2 subjects enrolled at the Moran Eye Center.

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Purpose: AREDS2 is a randomized, placebo-controlled study designed to determine whether supplementation with 10 mg of lutein and 2 mg of zeaxanthin per day can slow the rate of progression of age-related macular degeneration (AMD). Although some biomarkers of response to carotenoid supplementation such as serum concentrations are part of the AREDS2 protocol, measurement of carotenoid concentrations in the eye and other tissues is not. In this approved ancillary study, we measure macular pigment optical density (MPOD), macular pigment distributions, and skin carotenoid levels at enrollment and at each annual visit to assess baseline carotenoid status and to monitor response to assigned interventions.

Methods: All subjects enrolled at the Moran Eye Center had MPOD and macular pigment spatial distributions measured by dual-wavelength autofluorescence imaging and total skin carotenoids measured by resonance Raman spectroscopy.

Results: Baseline MPOD in enrolled subjects was unusually high relative to an age-matched control group which did not consume carotenoid supplements regularly, consistent with the high rate of habitual lutein and zeaxanthin consumption in Utah AREDS2 subjects prior to enrollment. MPOD did not correlate with serum or skin carotenoid measurements.

Conclusions: Our ancillary study provides useful information on the ocular carotenoid status of our site's AREDS2 participants in the target tissue of lutein and zeaxanthin supplementation, the macula of the human eye. When treatment assignments are unmasked at the conclusion of the study, we will be able to provide unique tissue-based insights on the progression of AMD in response to long-term, high-dose carotenoid supplementation versus diet alone.

PMID: 22879423 [PubMed - as supplied by publisher]

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