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MD Research News

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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

Br J Ophthalmol. 2013 Aug 21. doi: 10.1136/bjophthalmol-2013-303513. [Epub ahead of print]

Non-responders to treatment with antagonists of vascular endothelial growth factor in age-related macular degeneration.

Krebs I, Glittenberg C, Ansari-Shahrezaei S, Hagen S, Steiner I, Binder S.

The Ludwig Boltzmann Institute for Retinology and Biomicroscopic Laser Surgery, Vienna, Austria.

PURPOSE: Most of the publications on modern therapy of neovascular age-related macular degeneration focus on the effect of the treatment. The purpose of this study is to determine the frequency of non-responders to anti-vascular endothelial growth factor (anti-VEGF) treatment and find possible reasons for their failure to respond.

METHODS: The records of patients treated until the end of 2008 the first time with either bevacizumab or ranibizumab were reviewed. Based on the availability of measurable results and according to prior publications showing the effect of the therapy, loss of three lines of distance acuity, increase of retinal thickness or lesion size were identified as indicators of non-responders. Two of these three signs had to be present.

RESULTS: 334 eyes of 283 patients were included; 74.55% received bevacizumab and 25.45% received ranibizumab. Overall 14.37% of the eyes were identified as non-responders (14.06% in the bevacizumab group and 15.29% in the ranibizumab group). Baseline distance acuity and vitreo-retinal adhesions were significantly correlated with non-responders. Correlations with age, gender, lesion type, other morphologic features, and the kind of anti-VEGF agent failed to be significant. 10.4% of the non-responders showed a delayed but good response to anti-VEGF treatment.

CONCLUSIONS: About 15% did not sufficiently respond to anti-VEGF treatment. Vitreo-retinal adherences were the only ophthalmologic factor which could be identified to be significantly correlated with insufficient response.

PMID: 23966368 [PubMed - as supplied by publisher]

Int J Pharm Compd. 2008 Jan-Feb;12(1):9-14.

Intravitreal Bevacizumab for Choroidal Neovascularization in Age-Related Macular Degeneration.

Dib JG Bspharm Pharmd Ms, Abdulmohsin S Bspharm Ms.

Saudi Aramco Medical Services Organization, Dharan, Saudi Arabia.

Abstract: Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, is used in the treatment of cancer. It was the first clinically available angiogenesis inhibitor in the U.S. Recently, bevacizumab has been used by ophthalmologists in the intravitreal treatment of choroidal neovascularization in age-related macular degeneration. Since all published trials were less than one year in duration, including follow up, no conclusion can be drawn about the long-term safety and efficacy of intravitreal bevacizumab. In open-label studies, however, intravitreal bevacizumab has yielded marked improvements in visual acuity and central retinal thickness. Compounding pharmacists who are validated in aseptic compounding can prepare intravitreal bevacizumab from the available preservative-free phosphate-buffered intravenous solution using strict aseptic technique.

PMID: 23969568 [PubMed - as supplied by publisher]

Ophthalmologica. 2013 Aug 14. [Epub ahead of print]

Triple Therapy for Anti-Vascular Endothelial Growth Factor Nonresponders in Neovascular Age-Related Macular Degeneration: Impact of Different Photodynamic Therapy Parameters.

Veritti D, Lanzetta P.

Department of Ophthalmology, University of Udine, and Istituto Europeo di Microchirurgia Oculare, Udine, Italy.

Purpose: To evaluate the safety and exploratory efficacy of triple therapy (TT) with single-session intravitreal ranibizumab, modified juxtascleral triamcinolone, and photodynamic therapy (PDT) in exudative age-related macular degeneration non-responder to anti-vascular endothelial growth factor.

Methods: Thirty consecutive eyes were included. The first 10 eyes (cohort 1) enrolled received same-day TT with reduced-fluence/reduced-irradiance PDT, 10 eyes (cohort 2) received same-day TT with reduced-fluence/standard irradiance PDT, the last 10 eyes (cohort 3) received same-day TT with standard fluence/standard irradiance PDT.

Results: All patients completed the 6-month follow-up. Mean best corrected visual acuity (BCVA) at baseline was 1.1 (cohort 1), 0.9 (cohort 2) and 1.1 (cohort 3) logMAR. After 6 months, mean BCVA change was -0.15 (not significant), -0.13 (not significant) and 0.29 ($p < 0.05$) logMAR, respectively. Among eyes treated with standard fluence/standard irradiance PDT, 2 showed choroidal ischemia.

Conclusions: The combination of modified juxtascleral triamcinolone, reduced-fluence PDT, and ranibizumab appears as a safe treatment option.

PMID: 23948986 [PubMed - as supplied by publisher]

Semin Ophthalmol. 2013 Aug 16. [Epub ahead of print]

The Effect of Intravitreal Anti-VEGF on the Pigment Epithelial Detachment in Eyes with the Exudative Type of Age-Related Macular Degeneration.

Kalouda P, Anastasakis A, Tsika C, Tsilimbaris KM.

University of Crete Medical School, Department of Ophthalmology , Heraklion , Greece.

Abstract Purpose: To evaluate the effect of anti-VEGF treatment on pigment epithelial detachment (PED) secondary to the exudative type of age-related macular degeneration (AMD).

Methods: Retrospective analysis of 30 eyes (28 patients) with exudative AMD accompanied by PED

(receiving anti-VEGF injections). Alterations of the PED morphology were qualitatively assessed with optical coherence tomography (OCT). Changes in best-corrected visual acuity (BCVA) and number of injections were compared to 30 control eyes (30 patients) exhibiting exudative AMD without PED.

Results: Mean follow-up was 19.8 months. Changes of the extent of PED were as follows: unchanged: 11 eyes (36.7%); reduced: 12 (40%); significantly reduced: 7 (23.3%). Mean paired difference in BCVA was -0.08 logMAR ($p = 0.46$) and in the number of injections was 2.1 injections ($p = 0.04$).

Conclusions: A substantial number of the studied patients showed reduction of the extent of the PED after anti-VEGF treatment. The PED group required a higher number of injections.

PMID: 23952911 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Eye (Lond). 2013 Aug 23. doi: 10.1038/eye.2013.181. [Epub ahead of print]

Cognitive function, drusen, and age-related macular degeneration: a cross-sectional study.

Lindekleiv H, Erke MG, Bertelsen G, Peto T, Arntzen KA, Schirmer H, Wilsgaard T, Mathiesen EB, Njølstad I.

Faculty of Health Sciences, University of Tromsø, Tromsø, Norway.

Purpose: To examine the cross-sectional relationship between drusen, late age-related macular degeneration (AMD), and cognitive function.

Methods: We included 2149 stroke-free participants from the population-based Tromsø Study in Norway. Retinal photographs were graded for presence of drusen and AMD. Cognitive function was assessed using the verbal memory test (short verbal memory), digit-symbol coding test (processing speed), and the tapping test (psychomotor tempo). We assessed the relationship between drusen, late AMD, and cognitive test scores, adjusted for potential confounders.

Results: Late AMD was associated with decreased performance in the verbal memory test (standardized β=-0.23, 95% confidence interval (CI): -0.51 to -0.01). Intermediate and large drusen were associated with decreased performance in the digit-symbol coding test (standardized β=-0.14 and -0.19, 95% CIs: -0.23 to -0.05 and -0.29 to -0.09, respectively). Participants with large drusen were more likely to have test scores in the lowest quartile of the digit-symbol coding test (odds ratio (OR)=1.9, 95% CI: 1.1-3.5) and the tapping test (OR=1.6, 95% CI: 1.0-2.6), but not in the verbal memory test (OR=1.0, 95% CI: 0.6-1.6).

Conclusions: The findings suggest a relationship between drusen deposition and reduced cognitive function. Although the relationships between drusen, late AMD, and the cognitive test results varied in strength and significance across the types of cognitive test, and may partly have been caused by residual confounding, it is not unlikely that a genuine but weaker relationship exists between drusen deposition and cognitive decline.Eye advance online publication, 23 August 2013; doi:10.1038/eye.2013.181.

PMID: 23970030 [PubMed - as supplied by publisher]

Semin Ophthalmol. 2013 Aug 16. [Epub ahead of print]

Fundus Autofluorescence Imaging in Age-Related Macular Degeneration.

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Abstract: Fundus autofluorescence (FAF) is a noninvasive imaging technology that provides information on the distribution of lipofuscin within the retinal pigment epithelial cells. Progressive accumulation of lipofuscin within retinal pigment epithelial cells is involved in the pathogenesis of age-related macular degeneration (AMD). Fundus autofluorescence imaging using a confocal scanning laser ophthalmoscope is a useful technique to identify high-risk characteristics in patients with nonexudative AMD. It gives also some valuable knowledge and clues in differantial diagnosis of exudative age-related macular degeneration. This review comprises an introduction to fundus autofluorescence, a review of FAF imaging in AMD, and the recent classification of geographic atrophy (GA) and early AMD phenotypes by the Fundus Autofluorescence in Age-related Macular Degeneration Study. The association of phenotype and atrophy progression and choroidal neovascularization development are also summarized.

PMID: 23952079 [PubMed - as supplied by publisher]

Clin Interv Aging. 2013;8:1041-6. doi: 10.2147/CIA.S44834. Epub 2013 Aug 7.

Results of cataract surgery in the very elderly population.

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Department of Ophthalmology, University Hospital No 5, Medical University of Silesia, Katowice, Poland.

AIM: The aim of our study was to retrospectively evaluate the effectiveness and safety of cataract surgery and intraocular lens implantation (IOL) for patients aged 90 years or older, whom we define as "very elderly."

METHODS: The study involved a total number of 122 patients (122 eyes) with senile cataracts. The mean age of patients was 91.2 ± 2.3 years (range 90-100 years old). Phacoemulsification (phaco) was done on 113 of 122 eyes, and 9 of 122 eyes had extracapsular cataract extraction (ECCE). Postoperative visual acuity and intraocular pressure (IOP) were analyzed on the first postoperative day, 3 months after surgery, and 6 months after surgery.

RESULTS: Best corrected visual acuity (BCVA) improved in 100 of 122 eyes (82.0%). BCVA remained the same in 20 of 122 eyes (16.4%) and decreased in 2 of 122 eyes (1.6%), mainly because of coexisting age-related macular degeneration (AMD). The BCVA 3 months after surgery was ≥0.8 in 23 of 122 eyes (18.9%), between 0.5 and 0.7 in 28 of 122 eyes (22.3%), and between 0.2 and 0.4 in 33 of 122 eyes (27.1%). We found significant implications of cataract surgery on decreasing IOP in the studied group of patients suffering from glaucoma compared to the patients without glaucoma.

CONCLUSION: Advanced age is not a contraindication for cataract surgery. The results of the study showed that when systemic conditions are stable, both phaco and ECCE with IOL for very elderly patients are effective and safe.

PMID: 23966774 [PubMed - in process]

Psychiatr Q. 2013 Aug 21. [Epub ahead of print]

Ophthalmologic Screening in 25 Consecutive Geriatric Psychiatric Inpatient Admissions.

Billick SB, Garakani A.

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Abstract: In the aging process, people are at increasing risk of visual abnormalities such as cataracts, glaucoma, age-related macular degeneration, and other retinal defects. This holds true for geriatric

psychiatric patients as well. These ophthalmic problems may increase risk of falls or increase the comorbidity from dementing processes and depression. Geriatric patients presenting for psychiatric treatment may also be misdiagnosed or under-diagnosed as a result of these visual problems. This quality assurance review of 25 consecutive geriatric psychiatric inpatients demonstrated discrepancies between chart documentation and actual ophthalmologic pathology present in the patients. Doing a simple but complete ophthalmologic screening as part of the general physical examination on admission to an inpatient psychiatric unit can identify those patients who will need more in depth examination of their eyes and promote more accurate differential diagnoses for the patients.

PMID: 23963654 [PubMed - as supplied by publisher]

Saudi J Ophthalmol. 2011 Apr;25(2):145-58. doi: 10.1016/j.sjopt.2011.01.003. Epub 2011 Jan 26.

Predicting visual outcomes for macular disease using optical coherence tomography.

Keane PA, Sadda SR.

NIHR Biomedical Research Centre for Ophthalmology, Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, United Kingdom.

Abstract: In recent years, the management of macular disease has undergone radical changes, in part because of new therapeutic approaches, but also due to the introduction of a new imaging modality - optical coherence tomography (OCT). The application of OCT imaging has clarified many aspects of chorioretinal disease pathophysiology and elucidated many hitherto unrecognized disease characteristics. From an early stage in its development, OCT has also been revolutionary in attempting to extract clinically useful measurements from image data in an automated fashion. As a result, OCT-derived measurements of retinal thickness have been rapidly embraced in clinical and research settings. However, as knowledge of OCT image analysis has developed, it has become increasingly clear that even accurate measurements of retinal thickness may fail to predict visual outcomes for many diseases. As a result, the focus of much current clinical imaging research is on the identification of other OCT-derived anatomic biomarkers predictive of visual outcomes - such biomarkers could serve as surrogate endpoints in clinical trials and provide prognostic information in clinical practice. In this review, we begin by highlighting the importance of accurate visual function assessment and describing the fundamentals of OCT image evaluation, before describing the current state-of-the-art with regard to predicting visual outcomes, for a variety of macular diseases, using OCT.

PMID: 23960916 [PubMed]

Pathogenesis

Arch Biochem Biophys. 2013 Aug 19. pii: S0003-9861(13)00248-8. doi: 10.1016/j.abb.2013.08.005. [Epub ahead of print]

Similar molecules spatially correlate with lipofuscin and N-retinylidene-N-retinylethanolamine in the mouse but not in the human retinal pigment epithelium.

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Abstract: The accumulation of lipofuscin in the retinal pigment epithelium (RPE) has been implicated in the development of age-related macular degeneration (AMD) in humans. The exact composition of lipofuscin is not known but its best characterized component is N-retinylidene-N-retinylethanolamine (A2E), a byproduct

of the retinoid visual cycle. Utilizing our recently developed matrix-assisted laser desorption/ionization imaging mass spectrometry (MALDI-IMS)-based technique to determine the spatial distribution of A2E, this study compares the relationships of lipofuscin fluorescence and A2E in the murine and human RPE on representative normal tissue. To identify molecules with similar spatial patterns, the images of A2E and lipofuscin were correlated with all the individual images in the MALDI-IMS dataset. In the murine RPE, there was a remarkable correlation between A2E and lipofuscin. In the human RPE, however, minimal correlation was detected. These results were reflected in the marked distinctions between the molecules that spatially correlated with the images of lipofuscin and A2E in the human RPE. While the distribution of murine lipofuscin showed highest similarities with some of the known A2E-adducts, the composition of human lipofuscin was significantly different. These results indicate that A2E metabolism may be altered in the human compared to the murine RPE.

PMID: 23969078 [PubMed - as supplied by publisher]

J Biol Chem. 2013 Aug 22. [Epub ahead of print]

Pre-Treatment with Pyridoxamine Mitigates Isolevuglandin-Associated Retinal Effects in Mice Exposed to Bright Light.

Charvet CD, Saadane A, Wang M, Salomon RG, Brunengraber H, Turko IV, Pikuleva IA.

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Abstract: The benefits of antioxidant therapy for treating age-related macular degeneration, a devastating retinal disease, are limited. Perhaps species other than reactive oxygen intermediates should be considered as therapeutic targets. These could be lipid peroxidation products, including isolevuglandins (isoLGs), prototypical and extraordinarily reactive γ-ketoaldehydes that avidly bind to proteins, phospholipids, and DNA and modulate the properties of these biomolecules. We found IsoLG adducts in aged human retina but not in the retina of mice kept under dim lighting. Hence, to test whether scavenging of isoLGs could complement or supplant antioxidant therapy, we exposed mice to bright light and found that this insult leads to retinal isoLG-adduct formation. We then pre-treated mice with pyridoxamine - a B6 vitamer and efficient scavenger of γ-ketoaldehydes - and found that the levels of retinal isoLG adducts are decreased and morphological changes in photoreceptor mitochondria are not as pronounced as in untreated animals. Our study demonstrates that preventing the damage to biomolecules by lipid peroxidation products, a novel concept in vision research, is a viable strategy to combat oxidative stress in the retina.

PMID: 23970548 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 Aug 22. pii: iovs.13-11873v1. doi: 10.1167/iovs.13-11873. [Epub ahead of print]

Inhibitory Effect of MicroRNA-34a on Retinal Pigment Epithelial Cell Proliferation and Migration.

Hou Q, Tang J, Wang Z, Wang C, Chen X, Hou L, Dong XD, Tu L.

United States of America.

PURPOSE: Retinal pigment epithelial (RPE) cells play important roles in ophthalmologic diseases such as proliferative vitreoretinopathy, age-related macular degeneration and diabetic retinopathy. MicroRNA-34a (miR-34a) has been reported to be important in the regulation of cell proliferation, migration, differentiation and apoptosis. In this study, we explored the effects of miR-34a on RPE cells.

METHODS: The expression level of miR-34a in subconfluent and postconfluent ARPE-19 retinal epithelial

cells was investigated with quantitative real-time PCR. microRNA precursor and siRNA were transiently transfected into RPE cells. Transfected RPE cells were analyzed with WST-1 proliferation assay; and their migration was analyzed with transwell assay and in vitro scratch study. The expression or activation of target proteins was detected by Western blotting.

RESULTS: miR-34a was significantly downregulated in subconfluent ARPE-19 cells compared with postconfluent cells. Introduction of miR-34a inhibited the proliferation and migratory ability of RPE cells without obvious cell apoptosis. In miR-34a transfected cells, many important proliferation and/or migration related molecules such as c-Met, CDK2, CDK4, CDK6, E2F1, and p-Cdc2 were downregulated. siRNA designed to target c-Met also inhibited the proliferation and migration of RPE cells and downregulated CDK2, CDK6, E2F1 and p-Cdc2.

CONCLUSIONS: miR-34a is downregulated in subconfluent RPE cells. miR-34a can inhibit the proliferation and migration of RPE cells through downregulation of its targets c-Met and other cell cycle-related molecules. Our results indicated that miR-34a is involved in the regulation of RPE cells.

PMID: 23970470 [PubMed - as supplied by publisher]

Biogerontology. 2013 Aug 20. [Epub ahead of print]

Association of AMD-like retinopathy development with an Alzheimer's disease metabolic pathway in OXYS rats.

Kozhevnikova OS, Korbolina EE, Stefanova NA, Muraleva NA, Orlov YL, Kolosova NG.

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Abstract: The main cause of vision loss in older individuals is age-related macular degeneration (AMD)-a complex multifactorial disease, whose etiology and pathogenesis are not completely understood. This is due to the impossibility of investigating the early stages of AMD and paucity of biological models. The senescence-accelerated OXYS rats develop retinopathy with clinical and morphological manifestations similar to AMD. But the genetic determinants of its development are not known. Previously we identified quantitative trait loci (QTLs) associated with the development of cataract, retinopathy, and behavioral signs in OXYS rat. In this study, we used bioinformatic analysis to show the enrichment of QTL region with genes associated with neurodegeneration, including a pathway of Alzheimer's disease. For selected list of candidate genes we designed oligonucleotide DNA chips. Using them we found small but significant changes in expression of several genes in OXYS retina compared to disease-free Wistar rats. Among the genes with altered expression were Picalm and Apba2, known to be participants in the processing of the beta-amyloid (Aβ). Measurement of Aβ 1-42 in the retina showed that its level increases with age in rats, and at advanced stages of retinopathy in OXYS rats, its expression becomes significantly higher than that of disease-free Wistar rats. Based on functional annotation of QTL, microarray, and ELISA results we suggest that accumulation of Aβ may have a role in the pathogenesis of retinopathy in OXYS rats.

PMID: 23959258 [PubMed - as supplied by publisher]

Cell Death Differ. 2013 Aug 16. doi: 10.1038/cdd.2013.109. [Epub ahead of print]

Programmed necrosis, not apoptosis, is a key mediator of cell loss and DAMP-mediated inflammation in dsRNA-induced retinal degeneration.

Murakami Y, Matsumoto H, Roh M, Giani A, Kataoka K, Morizane Y, Kayama M, Thanos A, Nakatake S, Notomi S, Hisatomi T, Ikeda Y, Ishibashi T, Connor KM, Miller JW, Vavvas DG.

1] Department of Ophthalmology, Retina Service, Angiogenesis Laboratory, Massachusetts Eye and Ear

Infirmary, Harvard Medical School, Boston, MA, USA [2] Department of Ophthalmology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

Abstract: There is no known treatment for the dry form of an age-related macular degeneration (AMD). Cell death and inflammation are important biological processes thought to have central role in AMD. Here we show that receptor-interacting protein (RIP) kinase mediates necrosis and enhances inflammation in a mouse model of retinal degeneration induced by dsRNA, a component of drusen in AMD. In contrast to photoreceptor-induced apoptosis, subretinal injection of the dsRNA analog poly(I : C) caused necrosis of the retinal pigment epithelium (RPE), as well as macrophage infiltration into the outer retinas. In Rip3-/- mice, both necrosis and inflammation were prevented, providing substantial protection against poly(I : C)-induced retinal degeneration. Moreover, after poly(I : C) injection, Rip3-/- mice displayed decreased levels of pro-inflammatory cytokines (such as TNF-α and IL-6) in the retina, and attenuated intravitreal release of high-mobility group box-1 (HMGB1), a major damage-associated molecular pattern (DAMP). In vitro, poly(I : C)-induced necrosis were inhibited in Rip3-deficient RPE cells, which in turn suppressed HMGB1 release and dampened TNF-α and IL-6 induction evoked by necrotic supernatants. On the other hand, Rip3 deficiency did not modulate directly TNF-α and IL-6 production after poly(I : C) stimulation in RPE cells or macrophages. Therefore, programmed necrosis is crucial in dsRNA-induced retinal degeneration and may promote inflammation by regulating the release of intracellular DAMPs, suggesting novel therapeutic targets for diseases such as AMD.

PMID: 23954861 [PubMed - as supplied by publisher]

Anal Biochem. 2013 Aug 13. pii: S0003-2697(13)00381-3. doi: 10.1016/j.ab.2013.08.005. [Epub ahead of print]

Mass spectrometry quantification of PICALM and AP180 in human frontal cortex and neural retina.

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Abstract: Recent genome-wide association studies have suggested that endocytic factor, such as phosphatidylinositol-binding clathrin assembly protein (PICALM), may be implicated in the development of Alzheimer's disease (AD). The cellular functions of PICALM are in line with this possibility: (i) PICALM is involved in regulation of amyloid-β levels and (ii) PICALM is important for a pre-synaptic function, which is diminished in AD. To facilitate the analysis of PICALM, we developed a quantitative method to assess expression level of PICALM in different biological samples. For this purpose, a stable isotope-labeled quantification concatamer (QconCAT) of PICALM was designed, expressed, purified and characterized. The PICALM QconCAT was firstly used as an internal standard in a multiple reaction monitoring assay to measure PICALM concentrations in the human frontal cortex, tissue strongly affected by AD. A second endocytic factor which is highly homologous to PICALM and also functions in clathrin-mediated endocytosis, clathrin coat assembly protein AP180 (AP180), was quantified as well. Because age-related macular degeneration (AMD) shares several clinical and pathological features with AD, the measurements were then extended to human normal neural retina. Overall, the developed method is suitable for PICALM and AP180 quantitative analysis in various biological samples of interest.

PMID: 23954523 [PubMed - as supplied by publisher]

Exp Eye Res. 2013 Aug 15. pii: S0014-4835(13)00227-3. doi: 10.1016/j.exer.2013.07.023. [Epub ahead of print]

Novel compstatin family peptides inhibit complement activation by drusen-like deposits in human

retinal pigmented epithelial cell cultures.

Gorham RD Jr, Forest DL, Tamamis P, López de Victoria A, Kraszni M, Kieslich CA, Banna CD, Bellows-Peterson ML, Larive CK, Floudas CA, Archontis G, Johnson LV, Morikis D.

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Abstract: We have used a novel human retinal pigmented epithelial (RPE) cell-based model that mimics drusen biogenesis and the pathobiology of age-related macular degeneration to evaluate the efficacy of newly designed peptide inhibitors of the complement system. The peptides belong to the compstatin family and, compared to existing compstatin analogs, have been optimized to promote binding to their target, complement protein C3, and to enhance solubility by improving their polarity/hydrophobicity ratios. Based on analysis of molecular dynamics simulation data of peptide-C3 complexes, novel binding features were designed by introducing intermolecular salt bridge-forming arginines at the N-terminus and at position -1 of N-terminal dipeptide extensions. Our study demonstrates that the RPE cell assay has discriminatory capability for measuring the efficacy and potency of inhibitory peptides in a macular disease environment.

PMID: 23954241 [PubMed - as supplied by publisher]

Nat Rev Immunol. 2013 Sep;13(9):701. doi: 10.1038/nri3459-c1.

A role for IL-17 in age-related macular degeneration.

Shin JI, Bayry J.

Department of Pediatrics, Yonsei University College of Medicine, Seoul 120-752, Korea.

PMID: 23969738 [PubMed - in process]

Genetics

Hum Mol Genet. 2013 Aug 19. [Epub ahead of print]

Advances in the Genomics of Common Eye Diseases.

Cooke Bailey JN, Sobrin L, Pericak-Vance MA, Haines JL, Hammond CJ, Wiggs JL.

Center for Human Genetic Research, Vanderbilt University Medical Center, Nashville, TN, USA.

Abstract: Genome-wide association studies and other genomic technologies have accelerated the discovery of genes and genomic regions contributing to common human ocular disorders with complex inheritance. Age-related macular degeneration (AMD), diabetic retinopathy, glaucoma and myopia account for the majority of visual impairment worldwide. Over nineteen genes and/or genomic regions have been associated with AMD. Current investigations are assessing the clinical utility of risk score panels and therapies targeted disease-specific pathways. Diabetic retinopathy (DR) is the leading cause of blindness in the United States and globally is a major cause of vision loss. Genomic investigations have identified molecular pathways associated with DR in animal models which could suggest novel therapeutic targets. Three types of glaucoma, primary open angle glaucoma (POAG), angle-closure glaucoma and exfoliation syndrome glaucoma (XFS) are common age-related conditions. Five genomic regions have been associated with POAG, three with angle-closure glaucoma and one with XFS. Myopia causes substantial ocular morbidity throughout the world. Recent large GWAS have identified more than 20 associated loci for this condition. In this report we present a comprehensive overview of the genes and genomic regions contributing to disease susceptibility for these common blinding ocular disorders and discuss the next steps toward translation to effective gene-based screening tests and novel therapies targeting the molecular events contributing to disease.

PMID: 23962718 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2013 Aug 20. [Epub ahead of print]

ARMS2 interference leads to decrease of proinflammatory mediators.

Zeng F, Zhang M, Xu Y, Xu H.

Qingdao Eye Hospital, Shandong Eye Institute, Shandong Academy of Medical Sciences, 5 Yanerdao Road, Qingdao, 266071, China.

BACKGROUND: Age-related macular degeneration (AMD) is a major cause of irreversible blindness among elderly people in developed countries. Many studies suggested that age-related maculopathy susceptibility 2 (ARMS2) is the second major susceptibility gene for AMD. Increasing evidence was found recently that inflammatory processes and oxidative stress may contribute to the pathogenesis of AMD. Meanwhile, the mechanisms underlying the contributions of ARMS2 to the pathogenesis of AMD remain unclear. The purpose of the current study was to elucidate the relationship between the ARMS2 gene and proinflammatory mediators, for further assessment of the associated biologic effects.

METHODS: siRNA was used to knock down ARMS2 mRNA, and Western blotting and reverse real-time PCR were used to detect the effect of siRNA on the expression of ARMS2 in ARPE-19 cells. The expressions of C3, C5, IL-6, IL-8, and TNF-α after si-RNA knockdown were evaluated by SYBR Green I real-time PCR and ELISA.

RESULTS: Transcription accumulative indexes (TAI = 2-delta delta CT) of ARMS2 by real-time PCR revealed that the transfection rate in the positive control group was 72.0 ± 2.07 % ($P < 0.01$). The ratio of absorbance values (by Western blotting) of AMRS2 to β-actin was 0.85 ± 0.122, 0.87 ± 0.143, and 0.61 ± 0.240 in the blank control group, scrambled ARMS2-siRNA group, and ARMS2-siRNA group respectively ($F = 42.5$, $P < 0.01$). The secreted protein levels of C3, C5, IL-6, IL-8, and TNF-α were found by ELISA to be reduced by 34.24 ± 1.81 %, 37.15 ± 2.02 %, 35.11 ± 1.75 %, 30.11 ± 2.19 %, and 34.33 ± 2.18 % respectively, in the siRNA-ARMS2 group ($P < 0.05$). Compared with the blank control group, reduced TAI of C3, C5, IL-6, IL-8, and TNF-α were detected by real-time PCR in the ARMS2-siRNA group.

CONCLUSION: This study produced evidence supporting the notion that the ARMS2 risk allele for AMD is linked directly or indirectly to proinflammatory mediators. More importantly, our data indicate that the change in ARMS2 may affect C3, C5, IL-6, IL-8, and TNF-α levels, and this may be one of the mechanisms of AMD development.

PMID: 23959158 [PubMed - as supplied by publisher]

Diet

Evid Based Complement Alternat Med. 2013;2013:131306. doi: 10.1155/2013/131306. Epub 2013 Jul 22.

Antiangiogenic activity and pharmacogenomics of medicinal plants from traditional Korean medicine.

Seo EJ, Kuete V, Kadioglu O, Krusche B, Schröder S, Greten HJ, Arend J, Lee IS, Efferth T.

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Aim: In the present study, we investigated the antiangiogenic properties of 59 plants used in traditional Korean medicine. Selected phytochemicals were investigated in more detail for their modes of action.

Methods: A modified chicken-chorioallantoic-membrane (CAM) assay using quail eggs was applied to test for antiangiogenic effects of plant extracts. A molecular docking in silico approached the binding of plant

constituents to the vascular endothelial growth factor receptors 1 and 2 (VEGFR1, VEGFR2). Microarray-based mRNA expression profiling was employed to correlate the 50% inhibition concentrations (IC50) of a panel of 60 NCI cell lines to these phytochemicals.

Results: Extracts from Acer mono leaves, Reynoutria sachalniensis fruits, Cinnamomum japonicum stems, Eurya japonica leaves, Adenophora racemosa whole plant, Caryopteris incana leaves-stems, and Schisandra chinensis stems inhibited angiogenesis more than 50% in quail eggs. Selected phytochemicals from Korean plants were analyzed in more detail using microarray-based mRNA expression profiles and molecular docking to VEGFR1 and VEGFR2. These results indicate multifactorial modes of action of these natural products.

Conclusion: The antiangiogenic activity of plants used in traditional Korean medicine implicates their possible application for diseases where inhibition of blood vessel formation is desired, for example, cancer, macular degeneration, diabetic retinopathy and others.

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Curcumin analogue 1, 5-Bis (2-trifluoromethylphenyl)-1, 4-pentadien-3-one exhibit enhanced ability on Nrf2 activation and protection against acrolein-induced ARPE-19 cell toxicity.

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Abstract: Curcumin, a phytochemical agent in the spice turmeric, has received increasing attention for its anticancer, anti-inflammatory and antioxidant properties. However, application of curcumin have been limited due to its insolubility in water and poor bioavailability both clinically and experimentally. In addition, the protective effects and mechanisms of curcumin in eye diseases have been poorly studied. In the present study, we synthesized a curcumin analogue, 1, 5-Bis (2-trifluoromethylphenyl)-1, 4-pentadien-3-one (C3), which displayed improved protective effect against acrolein-induced toxicity in a human retinal pigment epithelial cell line (ARPE-19). At 5μM, curcumin completely protected against acrolein-induced cell oxidative damage and preserved GSH levels and mitochondrial function. Surprisingly, C3 displayed a complete protective effect at 0.5μM, which was much more efficient than curcumin. Both 0.5μM C3 and 5μM curcumin induced Nrf2 nuclear translocation and Nrf2 target genes transcription similarly. Experiments using Nrf2 siRNA showed that the protective effects of curcumin and C3 were eliminated by Nrf2 knockdown. Additionally, both curcumin and C3 activated the PI3/Akt pathway, however, Nrf2 activation was independent of this pathway, and therefore, we hypothesized that both curcumin and C3 activated phase II enzymes via directly disrupting the Nrf2/Keap1 complex and promoting Nrf2's nuclear translocation. Since acrolein challenge of ARPE-19 cells has been used as a model of smoking and age-related macular degeneration (AMD), we concluded that the curcumin analogue, C3, may be a more promising drug candidate for its potential application for the prevention and treatment of eye diseases, such as AMD.

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