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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 May 17. [Epub ahead of print]

Comparative toxicity and proliferation testing of aflibercept, bevacizumab and ranibizumab on different ocular cells.

Schnichels S, Hagemann U, Januschowski K, Hofmann J, Bartz-Schmidt KU, Szurman P, Spitzer MS, Aisenbrey S.

Centre of Ophthalmology, University Eye Hospital Tübingen, Tübingen, Germany.

BACKGROUND/AIMS: Vascular endothelial growth factor (VEGF) is a key factor in the pathogenesis of neovascular retinal diseases including age-related macular degeneration. VEGF inhibitors including ranibizumab, pegaptanib or bevacizumab improve retinal morphology and vision in many patients. The recently approved drug aflibercept (VEGF Trap-Eye/Eyelea, Regeneron, Tarrytown, New York, USA) offers a new therapy modality. We therefore tested for toxic and anti-proliferating effects of aflibercept.

METHODS: The effects of aflibercept (0.125, 0.5, 2 mg), ranibizumab (0.125 mg) and bevacizumab (0.3125 mg) after 1, 24, 48 and 72 h on cell morphology via phase contrast pictures, cell viability via MTS assay, total cell amount via crystal violet staining, apoptosis induction via caspase 3/7 assay and proliferation via BrdU assay were investigated. Three ocular cell lines were chosen for toxicology testing: ARPE19 cells, RGC-5 cells and 661W cells.

RESULTS: Aflibercept did not cause changes in cell morphology, induce apoptosis or cause permanent decrease in cell viability, cell density or proliferation in any cell line or concentration investigated. In general, aflibercept had fewer effects (upregulation or downregulation) compared with controls than bevacizumab or ranibizumab.

CONCLUSIONS: In our experiments, aflibercept did not lead to any negative effects on retinal cell lines and might therefore be used safely in clinical applications.

PMID: 23686000 [PubMed - as supplied by publisher]

JAMA Ophthalmol. 2013 May 9:1-6. doi: 10.1001/jamaophthalmol.2013.114. [Epub ahead of print]

Reading Speed Improvements in Retinal Vein Occlusion After Ranibizumab Treatment.

Suñer IJ, Bressler NM, Varma R, Lee P, Dolan CM, Ward J, Colman S, Rubio RG.

IMPORTANCE: Treatment of macular edema secondary to retinal vein occlusion with ranibizumab has been shown to improve visual acuity compared with macular laser or observation. It is important to determine whether these visual acuity improvements translate into measurable improvements in visual function.

OBJECTIVE: To examine the benefit of ranibizumab (Lucentis) on measured reading speed, a direct performance assessment, through 6 months in eyes of patients with macular edema after retinal vein occlusion (RVO).

DESIGN: Two multicenter, double-masked, phase 3 trials in which participants with macular edema after branch RVO or central RVO were randomized 1:1:1 to monthly sham, ranibizumab, 0.3 mg, or ranibizumab, 0.5 mg, for 6 months.

SETTING: Community- and academic-based ophthalmology practices specializing in retinal diseases.

PARTICIPANTS: Seven hundred eighty-nine eyes of 789 participants who were at least aged 18 years with macular edema secondary to retinal vein occlusion in the branch vein occlusion (BRAVO) and central vein occlusion (CRUISE) trials.

INTERVENTIONS: Eyes were randomized 1:1:1 to 1 of 3 groups for monthly injections for 6 months: sham (132 in BRAVO and 130 in CRUISE), intravitreal ranibizumab, 0.3 mg (134 in BRAVO and 132 in CRUISE), and intravitreal ranibizumab, 0.5 mg (131 in BRAVO and 130 in CRUISE). Patients were able to receive macular laser after 3 months if they met prespecified criteria.

MAIN OUTCOMES AND MEASURES: Reading speed in the study eye was measured with enlarged text (letter size equivalent to approximately 20/1500 at the test distance) at baseline and 1, 3, and 6 months. The number of correctly read words per minute (wpm) was reported. The reading speed test requires a sixth-grade reading level and does not account for literacy or cognitive state.

RESULTS: In patients with branch RVO, the mean gain for the 0.5-mg group was 31.3 wpm compared with 15.0 wpm in sham-treated eyes (difference, 16.3 wpm; P = .007) at 6 months. In patients with central RVO, the mean gain for the 0.5-mg group was 20.5 wpm compared with 8.1 wpm in sham-treated eyes (difference, 12.4 wpm; P = .01) at 6 months. A gain of 15 or more letters of best-corrected visual acuity letter score corresponded to an increase in reading speed of 12.3 wpm and 15.8 wpm in patients with branch and central RVO, respectively.

CONCLUSIONS AND RELEVANCE: These results suggest that patients with macular edema after RVO treated monthly with ranibizumab are more likely to have improvements in reading speed of the affected eyes through 6 months compared with sham treatment. These results demonstrate the relevance of the treatment benefit to functional visual gain.

PMID: 23699977 [PubMed - as supplied by publisher]

Diabetes. 2013 Jun;62(6):1808-1815.

Using the Past to Inform the Future: Anti-VEGF Therapy as a Road Map to Develop Novel Therapies for Diabetic Retinopathy.

Titchenell PM, Antonetti DA.

Department of Cellular and Molecular Physiology, Penn State University College of Medicine, Hershey, Pennsylvania.

Abstract: Therapies targeting vascular endothelial growth factor (VEGF) are revolutionizing the treatment of diabetic retinopathy (DR) and diabetic macular edema (DME). In August 2012, ranibizumab, a monoclonal antibody fragment targeting VEGF designed for ocular use, became the first and only U.S. Food and Drug

Administration-approved medical therapy for DME and the first approved treatment in over 25 years. This approval was based on strong preclinical data followed by numerous clinical trials that demonstrate an essential role of VEGF in vascular permeability and angiogenesis in both normal physiology and disease pathology. In this Perspective, we will examine the experimental studies and scientific data that aided in the success of the development of therapies targeting VEGF and consider how these approaches may inform the development of future therapeutics for diabetic eye disease. A multipoint model is proposed, based on well-established drug development principles, with the goal of improving the success of clinical drug development. This model suggests that to provide a validated preclinical target, investigators should demonstrate the following: the role of the target in normal physiology, a causal link to disease pathogenesis, correlation to human disease, and the ability to elicit clinically relevant improvements of disease phenotypes in animal models with multiple, chemically diverse interventions. This model will provide a framework to validate the current preclinical targets and identify novel targets to improve drug development success for DR.

PMID: 23704522 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2013 May 21. [Epub ahead of print]

Subconjunctival Palomid 529 in the treatment of neovascular age-related macular degeneration.

Dalal M, Jacobs-El N, Nicholson B, Tuo J, Chew E, Chan CC, Nussenblatt R, Ferris F, Meyerle C.

Laboratory of Immunology, National Eye Institute, National Institutes of Health, Bethesda, MD, USA.

BACKGROUND: Recent evidence suggests that neovascular age-related macular degeneration (AMD) may have an immune mediated component. Palomid 529, an investigational medication involving the immune Akt/mTOR pathway, is unique in dissociating both targets of rapamycin complexes TORC1 and TORC2. This small short-term pilot study assesses the safety of subconjunctival Palomid 529 in the treatment of neovascular AMD, with some limited efficacy information.

METHODS: In this 12-week phase I open-label prospective pilot study, five participants with neovascular age-related macular degeneration that were refractory to intravitreal anti-vascular endothelial growth factor (VEGF) received three serial monthly subconjunctival doses of 1.9 mg Palomid 529. All participants were also offered concomitant monthly intravitreal anti-VEGF injections. Safety was monitored via adverse events recording. Additional outcome measures included visual acuity, optical coherence tomography, fluorescein angiography, indocyanine green angiography and fundus photography.

RESULTS: The study drug was well-tolerated by all participants. There were no drug-related adverse events and no serious adverse events. A depot formed at the injection site, which persisted at the end of the study. In these anti-VEGF refractory patients, no clinically important changes in best-corrected visual acuity, fluorescein leakage pattern, choroidal neovascularization size on indocyanine green angiography, or autofluorescence pattern on fundus autofluorescence were observed compared to baseline. The fluid status, assessed with optical coherence tomography showed that central retinal thickness and macular volume remained stable in three participants, while the other two participants clinically progressed.

CONCLUSIONS: Serial subconjunctival injections of Palomid 529 were well-tolerated and resulted in depot formation. There were no concerns for any ocular or systemic toxicity during this small short-term study. Larger randomized studies are required to determine efficacy.

PMID: 23689994 [PubMed - as supplied by publisher]

Value Health. 2013 May;16(3):A177. doi: 10.1016/j.jval.2013.03.889. Epub 2013 May 3.

Cost-Effectiveness Of Intravitreal Aflibercept Injection (IAI) In Treating Neovascular Age-Related

Macular Degeneration In The US.

Vitti R, Clements KM, Panchmatia H, Hulbert E, Wittrup-Jensen K, Lewis BE.

Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA.

PMID: 23693602 [PubMed - in process]

Value Health. 2013 May;16(3):A176. doi: 10.1016/j.jval.2013.03.884. Epub 2013 May 3.

Budgetary Impact Of Intravitreal Aflibercept Injection (IAI) In Treating Neovascular Age-Related Macular Degeneration In A US Health Plan Of Adults Ages 65 Years And Older.

Vitti R, Clements KM, Panchmatia H, Hulbert E, Wittrup-Jensen K, Lewis BE.

Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA.

PMID: 23693594 [PubMed - in process]

Value Health. 2013 May;16(3):A175-6. doi: 10.1016/j.jval.2013.03.881. Epub 2013 May 3.

Comparing Treatment Patterns And Efficacy Of Ranibizumab For Patients With Age-Related Macular Degeneration (AMD): A Meta-Analysis.

Jiang S, Park C, Barner JC.

The University of Texas at Austin, Austin, TX, USA.

PMID: 23693587 [PubMed - in process]

Other treatment & diagnosis

Curr Drug Targets. 2013 May 21. [Epub ahead of print]

Hypoxia-Inducible Factor-1 (HIF-1): A Potential Target for Intervention in Ocular Neovascular Diseases.

Vadlapatla RK, Vadlapudi AD, Mitra AK.

University of Missouri-Kansas City, School of Pharmacy, 2464 Charlotte Street, Kansas City, MO 64108-2718, USA. mitraa@umkc.edu.

Abstract: Constant oxygen supply is essential for proper tissue development, homeostasis and function of all eukaryotic organisms. Cellular response to reduced oxygen levels is mediated by the transcriptional regulator hypoxia-inducible factor-1 (HIF-1). It is a heterodimeric complex protein consisting of an oxygen dependent subunit (HIF-1α) and a constitutively expressed nuclear subunit (HIF-1β). In normoxic conditions, de novo synthesized cytoplasmic HIF-1α is degraded by 26S proteasome. Under hypoxic conditions, HIF-1α is stabilized, binds with HIF-1β and activates transcription of various target genes. These genes play a key role in regulating angiogenesis, cell survival, proliferation, chemotherapy, radiation resistance, invasion, metastasis, genetic instability, immortalization, immune evasion, metabolism and stem cell maintenance. This review highlights the importance of hypoxia signaling in development and progression of various vision threatening pathologies such as diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration and glaucoma. Further, various inhibitors of HIF-1 pathway that may have a viable potential in the treatment of oxygen-dependent ocular diseases are also discussed.

PMID: 23701276 [PubMed - as supplied by publisher]

Biochemistry. 2013 May 23. [Epub ahead of print]

The functional anatomy of complement factor H.

Makou E, Herbert AP, Barlow PN.

Abstract: Factor H (FH) is a soluble regulator of the proteolytic cascade at the core of the evolutionarily ancient vertebrate complement system. Although FH consists of a single chain of similar protein modules, it has a demanding job description. Its chief role is to prevent complement-mediated injury to healthy host cells and tissues. This entails recognition of molecular patterns on host surfaces combined with control of one of nature's most dangerous examples of a positive-feedback loop. In this way, FH modulates, where and when needed, an amplification process that otherwise exponentially escalates production of the pro-inflammatory, pro-phagocytic and pro-cytolytic cleavage products of complement proteins C3 and C5. Mutations and single-nucleotide polymorphisms in the FH gene and autoantibodies against FH predispose to diseases including age-related macular degeneration, dense-deposit disease and atypical hemolytic uremic syndrome. Moreover, deletions or variations of genes for FH-related proteins also influence the risk of disease. Numerous pathogens hijack FH and use it for self-defense. As reviewed herein, a molecular understanding of FH function is emerging. While its functional oligomeric status remains uncertain, progress has been achieved in characterising its three-dimensional architecture and, to a lesser extent, its inter-modular flexibility. Models are proposed, based on reconciliation of older data with a wealth of recent evidence, in which a latent circulating form of FH is activated by its principal target, C3b tethered to a self-surface. Such models suggest hypotheses linking sequence variations to pathophysiology but improved, more quantitative, functional assays and rigorous data analysis are required to test these ideas.

PMID: 23701234 [PubMed - as supplied by publisher]

Rev Med Chir Soc Med Nat Iasi. 2012 Oct-Dec;116(4):1136-42.

Use of blood markers in early diagnosis of oxidative stress in age related macular degeneration.

Dănulescu R, Costin D.

University of Medicine and Pharmacy Grigore T Popa Iasi, Faculty of Medicine.

AIM: To establish the role of oxidative stress in retinal structural lesions.

MATERIALS AND METHODS: It is a case-control study that included 19 patients diagnosed with AMD. Depending on the severity of the diagnosis, patients were divided into 3 groups: group 1 - mild AMD, group 2 - moderate, atrophic AMD, group 3 - severe, neovascular AMD. They were followed by assessment of visual acuity, optical coherence tomography (OCT) and oxidative stress markers like superoxide-dismutase (SOD), thiobarbituric acid reactive substances (TBARS) and inflammatory marker - C-reactive protein (CRP). Results: Risk factors involved in patients with AMD are arterial hypertension, smoking, hyperlipidemia and diet poor in antioxidants, as revealed in the questionnaire. Retinal thickness assessed by optical coherence tomography showed that values in patients with severity level 2 is within normal limits, while in patients with severity level 3, these values are significantly increased due to macular edema. The mean values of SOD, TBARS and CRP in the studied group were significantly higher compared to controls, being higher in group severity level 3.

CONCLUSIONS: This study shows the role of oxidative stress and inflammation in retinal structural lesions in AMD and the importance of blood markers in early detection of oxidative stress and thus of retinal lesions in this disease.

PMID: 23700902 [PubMed - in process]

Ophthalmology. 2013 May 15. pii: S0161-6420(13)00151-6. doi: 10.1016/j.ophtha.2013.02.017. [Epub ahead of print]

Electronic Health Record Systems in Ophthalmology: Impact on Clinical Documentation.

Sanders DS, Lattin DJ, Read-Brown S, Tu DC, Wilson DJ, Hwang TS, Morrison JC, Yackel TR, Chiang MF.

Department of Ophthalmology, Casey Eye Institute, Oregon Health & Science University, Portland, Oregon.

OBJECTIVE: To evaluate quantitative and qualitative differences in documentation of the ophthalmic examination between paper and electronic health record (EHR) systems.

DESIGN: Comparative case series.

PARTICIPANTS: One hundred fifty consecutive pairs of matched paper and EHR notes, documented by 3 attending ophthalmologist providers.

METHODS: An academic ophthalmology department implemented an EHR system in 2006. Database queries were performed to identify cases in which the same problems were documented by the same provider on different dates, using paper versus EHR methods. This was done for 50 consecutive pairs of examinations in 3 different diseases: age-related macular degeneration (AMD), glaucoma, and pigmented choroidal lesions (PCLs). Quantitative measures were used to compare completeness of documenting the complete ophthalmologic examination, as well as disease-specific critical findings using paper versus an EHR system. Qualitative differences in paper versus EHR documentation were illustrated by selecting representative paired examples.

MAIN OUTCOME MEASURES: (1) Documentation score, defined as the number of examination elements recorded for the slit-lamp examination, fundus examination, and complete ophthalmologic examination and for critical clinical findings for each disease. (2) Paired comparison of qualitative differences in paper versus EHR documentation.

RESULTS: For all 3 diseases (AMD, glaucoma, PCL), the number of complete examination findings recorded was significantly lower with paper than the EHR system (P≤0.004). Among the 3 individual examination sections (general, slit lamp, fundus) for the 3 diseases, 5 of the 9 possible combinations had significantly lower mean documentation scores with paper than EHR notes. For 2 of the 3 diseases, the number of critical clinical findings recorded was significantly lower using paper versus EHR notes (P≤0.022). All (150/150) paper notes relied on graphical representations using annotated hand-drawn sketches, whereas no (0/150) EHR notes contained drawings. Instead, the EHR systems documented clinical findings using textual descriptions and interpretations.

CONCLUSIONS: There were quantitative and qualitative differences in the nature of paper versus EHR documentation of ophthalmic findings in this study. The EHR notes included more complete documentation of examination elements using structured textual descriptions and interpretations, whereas paper notes used graphical representations of findings.

PMID: 23683945 [PubMed - as supplied by publisher]

Pathogenesis

Int J Mol Sci. 2013 May 17;14(5):10355-68. doi: 10.3390/ijms140510355.

Ultraviolet (UV) and Hydrogen Peroxide Activate Ceramide-ER Stress-AMPK Signaling Axis to Promote Retinal Pigment Epithelium (RPE) Cell Apoptosis.

Yao J, Bi HE, Sheng Y, Cheng LB, Wendu RL, Wang CH, Cao GF, Jiang Q.

The Affiliated Eye Hospital of Nanjing Medical University, Nanjing 210029, China. dryaojin@yahoo.com.

Abstract: Ultraviolet (UV) radiation and reactive oxygen species (ROS) impair the physiological functions of retinal pigment epithelium (RPE) cells by inducing cell apoptosis, which is the main cause of age-related macular degeneration (AMD). The mechanism by which UV/ROS induces RPE cell death is not fully addressed. Here, we observed the activation of a ceramide-endoplasmic reticulum (ER) stress-AMP activated protein kinase (AMPK) signaling axis in UV and hydrogen peroxide (H2O2)-treated RPE cells. UV and H2O2 induced an early ceramide production, profound ER stress and AMPK activation. Pharmacological inhibitors against ER stress (salubrinal), ceramide production (fumonisin B1) and AMPK activation (compound C) suppressed UV- and H2O2-induced RPE cell apoptosis. Conversely, cell permeable short-chain C6 ceramide and AMPK activator AICAR (5-amino-1-β-D-ribofuranosyl-imidazole-4-carboxamide) mimicked UV and H2O2's effects and promoted RPE cell apoptosis. Together, these results suggest that UV/H2O2 activates the ceramide-ER stress-AMPK signaling axis to promote RPE cell apoptosis.

PMID: 23685869 [PubMed]

FEBS Lett. 2013 May 15. pii: S0014-5793(13)00362-1. doi: 10.1016/j.febslet.2013.05.020. [Epub ahead of print]

The cell stress machinery and retinal degeneration.

Athanasiou D, Aguilà M, Bevilacqua D, Novoselov SS, Parfitt DA, Cheetham ME.

UCL Institute of Ophthalmology, 11-43 Bath Street, London EC1V 9EL, UK.

Abstract: Retinal degenerations are a group of clinically and genetically heterogeneous disorders characterised by progressive loss of vision due to neurodegeneration. The retina is a highly specialised tissue with a unique architecture and maintaining homeostasis in all the different retinal cell types is crucial for healthy vision. The retina can be exposed to a variety of environmental insults and stress, including light -induced damage, oxidative stress and inherited mutations that can lead to protein misfolding. Within retinal cells there are different mechanisms to cope with disturbances in proteostasis, such as the heat shock response, the unfolded protein response and autophagy. In this review, we discuss the multiple responses of the retina to different types of stress involved in retinal degenerations, such as retinitis pigmentosa, age-related macular degeneration and glaucoma. Understanding the mechanisms that maintain and re-establish proteostasis in the retina is important for developing new therapeutic approaches to fight blindness.

PMID: 23684651 [PubMed - as supplied by publisher]

PLoS One. 2013 May 21;8(5):e64619. Print 2013.

Inflammatory Cytokines Protect Retinal Pigment Epithelial Cells from Oxidative Stress-Induced Death.

Juel HB, Faber C, Svendsen SG, Vallejo AN, Nissen MH.

Eye Research Unit, Department of International Health, Immunology and Microbiology, University of Copenhagen, Copenhagen, Denmark.

PURPOSE: To investigate the effects of inflammatory factors and oxidative stress on cell survival of the human retinal pigment epithelial (RPE) cell line, ARPE-19.

METHODS: Confluent RPE cells were treated with peripheral blood mononuclear cells-conditioned medium (PCM), H2O2, NaIO3, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, or combinations of these. Cell viability was determined by viability assays and by light microscopy. Effector molecules of cell death were investigated by immunofluorescence microscopy and flow cytometry. Microarrays were performed to screen

for differential expression of anti-oxidative enzymes, and protein expression was validated by immunoblotting.

RESULTS: Viability of RPE cells was reduced by exposure to inflammatory agents (PCM, IFNγ+/-TNFα) or to oxidative agents (H2O2 or NaIO3). Unexpectedly, cells treated with either H2O2 or NaIO3 were partially protected from cell death by the addition of PCM. This protection was conferred, at least in part, by IFNγ and TNFα. Cell death induced by H2O2 or NaIO3 was preceded by mitochondrial dysfunction and by p62 upregulation, both of which were attenuated by PCM and/or by IFNγ+TNFα. RPE cells co-cultured with activated T cells, or treated with cytokines showed increased expression of anti-oxidative genes, with upregulation of superoxide dismutase 2 protein following PCM treatment.

CONCLUSION: Oxidative stress-induced cell death was reduced by concomitant inflammatory stress. This is likely due to the cytokine-mediated induction of the anti-oxidative stress response, upregulating protective anti-oxidant pathway(s). These findings suggest caution for the clinical use of anti-inflammatory agents in the management of immune-associated eye diseases such as age-related macular degeneration.

PMID: 23705001 [PubMed - as supplied by publisher]

Nat Rev Immunol. 2013 May 24;13(6):438-451. doi: 10.1038/nri3459.

Immunology of age-related macular degeneration.

Ambati J, Atkinson JP, Gelfand BD.

[1] Department of Ophthalmology and Visual Sciences, University of Kentucky, Lexington, Kentucky 40506, USA. [2] Department of Physiology, University of Kentucky, Lexington, Kentucky 40506, USA.

Abstract: Age-related macular degeneration (AMD) is a leading cause of blindness in aged individuals. Recent advances have highlighted the essential role of immune processes in the development, progression and treatment of AMD. In this Review we discuss recent discoveries related to the immunological aspects of AMD pathogenesis. We outline the diverse immune cell types, inflammatory activators and pathways that are involved. Finally, we discuss the future of inflammation-directed therapeutics to treat AMD in the growing aged population.

PMID: 23702979 [PubMed - as supplied by publisher]

Exp Eye Res. 2013 May 20. pii: S0014-4835(13)00125-5. doi: 10.1016/j.exer.2013.05.006. [Epub ahead of print]

Antiangiogenic effects of tivozanib, an oral VEGF receptor tyrosine kinase inhibitor, on experimental choroidal neovascularization in mice.

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Abstract: We investigated the effects of tivozanib, an oral vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor, on experimental choroidal neovascularization (CNV) in mice. C57BL/6 mice were treated with tivozanib (1 mg/kg/day) or vehicle at the onset (day 0) of the study and experimental CNV was induced by laser photocoagulation the following day. In the other groups, tivozanib or vehicle was started 7 days after the laser photocoagulation to determine the effects of the drug on established CNV. To evaluate changes in the CNV lesions, choroidal flat mounts, fluorescein angiography, immunofluorescence

staining with isolectin B4, and histological examinations were performed 14 days after CNV induction. Expression of phosphorylated ERK1/2 in choroidal tissues was measured by western blot analysis to demonstrate the inhibitory effect of tivozanib on intracellular signaling pathways involved in CNV development. Compared to vehicle-treatment, tivozanib suppressed the development of CNV lesions and led to a significant regression of established CNV, reducing the affected areas by 80.7 % and 67.7 %, respectively. On fluorescein angiography, tivozanib-treated mice had significantly less fluorescence leakage than vehicle-treated mice ($P < 0.001$). On immunofluorescence staining, the isolectin B4-labeled area was smaller in tivozanib-treated mice ($P < 0.001$). Phosphorylated ERK 1/2 levels increased after CNV induction by laser application and were suppressed by tivozanib treatment. Tivozanib effectively inhibited the progression of CNV in an experimental CNV model. These results suggest that tivozanib may be a therapeutic alternative for the treatment of neovascular age-related macular degeneration.

PMID: 23701975 [PubMed - as supplied by publisher]

Epidemiology

Value Health. 2013 May;16(3):A179. doi: 10.1016/j.jval.2013.03.897. Epub 2013 May 3.

Patient burden associated with wet age-related macular degeneration in Japan.

Adachi K, Wang EC, Kudo K, Crawford B, Fujita K, Nagai Y, Arisawa A, Hiramoto Y, Fujii S, Uda S, Takahashi K, Yuzawa M.

Bayer Yakuhin, Ltd., Tokyo, Japan.

PMID: 23693612 [PubMed - in process]

Genetics

Nat Genet. 2013 May 19. doi: 10.1038/ng.2640. [Epub ahead of print]

A functional variant in the CFI gene confers a high risk of age-related macular degeneration.

van de Ven JP, Nilsson SC, Tan PL, Buitendijk GH, Ristau T, Mohlin FC, Nabuurs SB, Schoenmaker-Koller FE, Smailhodzic D, Campochiaro PA, Zack DJ, Duvvari MR, Bakker B, Paun CC, Boon CJ, Uitterlinden AG, Liakopoulos S, Klevering BJ, Fauser S, Daha MR, Katsanis N, Klaver CC, Blom AM, Hoyng CB, den Hollander AI.

1] Department of Ophthalmology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands. [2].

Abstract: Up to half of the heritability of age-related macular degeneration (AMD) is explained by common variants. Here, we report the identification of a rare, highly penetrant missense mutation in CFI encoding a p.Gly119Arg substitution that confers high risk of AMD ($P = 3.79 \times 10\text{-}6$; odds ratio (OR) = 22.20, 95% confidence interval (CI) = 2.98-164.49). Plasma and sera from cases carrying the p.Gly119Arg substitution mediated the degradation of C3b, both in the fluid phase and on the cell surface, to a lesser extent than those from controls. Recombinant protein studies showed that the Gly119Arg mutant protein is both expressed and secreted at lower levels than wild-type protein. Consistent with these findings, human CFI mRNA encoding Arg119 had reduced activity compared to wild-type mRNA encoding Gly119 in regulating vessel thickness and branching in the zebrafish retina. Taken together, these findings demonstrate that rare, highly penetrant mutations contribute to the genetic burden of AMD.

PMID: 23685748 [PubMed - as supplied by publisher]

Eur J Hum Genet. 2013 May 22. doi: 10.1038/ejhg.2013.92. [Epub ahead of print]

Stargardt disease: towards developing a model to predict phenotype.

Heathfield L, Lacerda M, Nossek C, Roberts L, Ramesar RS.

UCT/MRC Human Genetics Research Unit, Division of Human Genetics, Institute of Infectious Diseases and Molecular Medicine, Faculty of Health Science, University of Cape Town, Cape Town, South Africa.

Abstract: Stargardt disease is an ABCA4-associated retinopathy, which generally follows an autosomal recessive inheritance pattern and is a frequent cause of macular degeneration in childhood. ABCA4 displays significant allelic heterogeneity whereby different mutations can cause retinal diseases with varying severity and age of onset. A genotype-phenotype model has been proposed linking ABCA4 mutations, purported ABCA4 functional protein activity and severity of disease, as measured by degree of visual loss and the age of onset. It has, however, been difficult to verify this model statistically in observational studies, as the number of individuals sharing any particular mutation combination is typically low. Seven founder mutations have been identified in a large number of Caucasian Afrikaner patients in South Africa, making it possible to test the genotype-phenotype model. A generalised linear model was developed to predict and assess the relative pathogenic contribution of the seven mutations to the age of onset of Stargardt disease. It is shown that the pathogenicity of an individual mutation can differ significantly depending on the genetic context in which it occurs. The results reported here may be used to identify suitable candidates for inclusion in clinical trials, as well as guide the genetic counselling of affected individuals and families.European Journal of Human Genetics advance online publication, 22 May 2013; doi:10.1038/ejhg.2013.92.

PMID: 23695285 [PubMed - as supplied by publisher]

Mol Vis. 2013 May 1;19:944-54. Print 2013.

No association of age-related maculopathy susceptibility protein 2/HtrA serine peptidase 1 or complement factor H polymorphisms with early age-related maculopathy in a Chinese cohort.

Chen JH, Yang Y, Zheng Y, Qiu M, Xie M, Lin W, Zhang M, Pang CP, Chen H.

Joint Shantou International Eye Center, Shantou University & the Chinese University of Hong Kong, Shantou, China ; Department of Ophthalmology and Visual Sciences, the Chinese University of Hong Kong, Hong Kong, China.

PURPOSE: Single nucleotide polymorphisms (SNPs) of age-related maculopathy susceptibility protein 2/ HtrA serine peptidase 1 (ARMS2/HTRA1) and complement factor H (CFH) have been reported to be associated with age-related macular degeneration (AMD). The purpose of this study was to investigate the association of ARMS2/HTRA1 and CFH SNPs with early age-related maculopathy (ARM) in a Han Chinese cohort.

METHODS: The cohort consisted of 315 unrelated subjects, including 158 patients with early ARM and 157 recruited controls. Early ARM was diagnosed and graded according to the Age-Related Eye Disease Study criteria. Four SNPs in ARMS2/HTRA1 and six SNPs in CFH previously reported to be associated with AMD were genotyped using TaqMan genotyping assays. Logistic regression implemented with the R statistical language was used for association analysis.

RESULTS: None of the ARMS2/HTRA1 and CFH SNPs showed any significant association with early ARM (all p>0.453), with the odds ratios ranging from 0.88 to 1.17. None of the SNPs were associated with unilateral or bilateral early ARM or any grade of early ARM (all p>0.249).

CONCLUSIONS: The association of ARMS2/HTRA1 and CFH SNPs in early ARM was not detected in our cohort. The findings in the current study indicated that the effects of ARMS2/HTRA1 and CFH in early ARM

could be much lower compared to those in AMD.

PMID: 23687431 [PubMed - in process] PMCID: PMC3654849

Diet

Graefes Arch Clin Exp Ophthalmol. 2013 May 22. [Epub ahead of print]

Long term effects of lutein, zeaxanthin and omega-3-LCPUFAs supplementation on optical density of macular pigment in AMD patients: the LUTEGA study.

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BACKGROUND: The primary objective of LUTEGA is to determine the long-term effect of a supplementation with fixed combination of lutein, zeaxanthin, omega-3-longchain-polyunsaturated-fatty-acids (O-3-LCPUFAs) and antioxidants on macular pigment optical density (MPOD) in patients with non-exudative age-related macular degeneration (AMD).

METHODS: The LUTEGA study is a double-blind, placebo-controlled clinical trial. 172 patients with non-exudative AMD were enrolled and randomized to three treatment arms. Supplementation included either once (dosage D1) or twice daily (dosage D2) of 10 mg L / 1 mg Z/ O-3-LCPUFAs (thereof 100 mg DHA, 30 mg EPA)/ antioxidants, or placebo (P). After best-corrected visual acuity (BCVA) test, blood sample was collected and MPOD was measured using the 1-wavelength-reflection method and recording reflection images at 480 nm (modified VisucamNM/FA, Carl Zeiss Meditec, Germany). During 1 year of intervention, AMD patients were followed up after 1, 3, 6 and 12 months. 145 AMD patients (D1 = 50, D2 = 55, P = 40) completed the study.

RESULTS: After 12 months of intervention, the MPOD parameters (volume, area, maxOD, meanOD) increased significantly in treatment arms D1 and D2 ($p < 0.001$). Volume of MPOD showed the highest within-group difference and increased significantly in D1 and D2, and decreased significantly in P ($p = 0.041$). Between-group comparison of absolute changes of all MPOD parameters were significantly different between D1 and P as well as D2 and P with $p < 0.001$ at end point ($t = 12$). BCVA, measured in log MAR, improved in D1 and in D2 ($p < 0.001$). After 12 months of intervention, the mean improvement in BCVA was significant in D2 ($p = 0.006$) and D1 ($p = 0.038$) compared to P.

CONCLUSIONS: The supplementation of L, Z, O-3-LCPUFAs and antioxidants resulted in considerable increase in MPOD. There was no difference in accumulation of MPOD between both dosages. Thus, we believe that the used supplementation with L and Z seems to reach a saturation level in retinal cell structure. Additionally, the constant supplementation of L, Z, O-3-LCPUFAs and antioxidants in AMD patients seems to be useful, because MPOD reduces without supplementation. We conclude that the supplementation caused an increase of MPOD, which results in an improvement and stabilization in BCVA in AMD patients. Thus, a protective effect on the macula in AMD patients is assumed.

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The role of lutein in eye-related disease.

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Abstract: The lens and retina of the human eye are exposed constantly to light and oxygen. In situ phototransduction and oxidative phosphorylation within photoreceptors produces a high level of phototoxic and oxidative related stress. Within the eye, the carotenoids lutein and zeaxanthin are present in high concentrations in contrast to other human tissues. We discuss the role of lutein and zeaxanthin in ameliorating light and oxygen damage, and preventing age-related cellular and tissue deterioration in the eye. Epidemiologic research shows an inverse association between levels of lutein and zeaxanthin in eye tissues and age related degenerative diseases such as macular degeneration (AMD) and cataracts. We examine the role of these carotenoids as blockers of blue-light damage and quenchers of oxygen free radicals. This article provides a review of possible mechanisms of lutein action at a cellular and molecular level. Our review offers insight into current clinical trials and experimental animal studies involving lutein, and possible role of nutritional intervention in common ocular diseases that cause blindness.

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What is meso-zeaxanthin, and where does it come from?

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Abstract: The carotenoids lutein (L), zeaxanthin (Z), and meso-zeaxanthin (MZ) accumulate in the central retina, where they are collectively known as macular pigment (MP). Each of these three compounds exhibit a regional dominance, with MZ, Z, and L being the dominant carotenoids at the epicentre, mid-periphery, and periphery of the macula, respectively. There is a growing and evidence-based consensus that MP is important for optimal visual performance, because of its blue light-filtering properties and consequential attenuation of chromatic aberration, veiling luminance, and blue haze. It has also been hypothesised that MP may protect against age-related macular degeneration because of the same optical properties and also because of the antioxidant capacity of the three macular carotenoids. Challenges inherent in the separation and quantification of MZ have resulted in a paucity of data on the content of this carotenoid in foodstuffs, and have rendered the study of tissue concentrations of this compound problematic. As a consequence, the few studies that have investigated MZ have, perhaps, been disproportionately influential in the ongoing debate about the origins of this macular carotenoid. Certainly, the narrative that retinal MZ is derived wholly and solely from retinal L needs to be revisited.Eye advance online publication, 24 May 2013; oi:10.1038/eye.2013.98.

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