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MD Research News

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Drug treatment

Retina. 2012 Jun 20. [Epub ahead of print]

TOPICAL BROMFENAC AS AN ADJUNCTIVE TREATMENT WITH INTRAVITREAL RANIBIZUMAB FOR EXUDATIVE AGE-RELATED MACULAR DEGENERATION.

Gomi F, Sawa M, Tsujikawa M, Nishida K.

Department of Ophthalmology, Osaka University Graduate School of Medicine, Osaka, Japan.

PURPOSE: Intravitreal injection of ranibizumab is highly effective for wet age-related macular degeneration. Its limitation is that most patients require repeated intravitreal injections to achieve and maintain the visual gain. We assessed the effectiveness of adjunctive topical bromfenac, a nonsteroidal antiinflammatory drug, with ranibizumab.

METHODS: Patients with wet age-related macular degeneration with lesions smaller than 2 disk diameters were randomized 2:3 to adjunctive topical bromfenac (n = 16) or sham (n = 22) and a 0.5-mg ranibizumab injection in a double-masked fashion. Subjects were examined monthly, and ranibizumab was injected as needed from baseline. The primary endpoint was the comparison of the number of ranibizumab injections over 6 months. The visual and anatomic responses also were compared.

RESULTS: The mean number of ranibizumab injections over 6 months was 2.2 in the bromfenac group and 3.2 in the sham, a difference that reached significance (P = 0.0274). The changes in visual acuity did not differ significantly (P = 0.3141) although the central retinal thickness was tended to decrease more in bromfenac group (P = 0.0604). Multivariate analysis showed that topical bromfenac is significantly associated with fewer ranibizumab injections.

CONCLUSION: Topical bromfenac might reduce the frequency of ranibizumab over 6 months in eyes with relatively small age-related macular degeneration lesions.

PMID: 22718152 [PubMed - as supplied by publisher]

Ophthalmology. 2012 Jun 19. [Epub ahead of print]

Stroke Rates after Introduction of Vascular Endothelial Growth Factor Inhibitors for Macular Degeneration: A Time Series Analysis.

Campbell RJ, Bell CM, Paterson JM, Bronskill SE, Moineddin R, Whitehead M, Gill SS.

Department of Ophthalmology, Queen's University, Kingston, Canada; Institute for Clinical Evaluative Sciences, Ontario, Canada; Department of Ophthalmology, Hotel Dieu Hospital, Kingston, Canada.

OBJECTIVE: To assess whether stroke rates among patients with retinal disease were influenced by the rapid and sequential uptakes of bevacizumab and ranibizumab for age-related macular degeneration (AMD).

DESIGN: Population-based, time series analysis using encrypted, linked healthcare databases in Ontario, Canada.

PARTICIPANTS: We included all patients aged 66 years or older with physician-diagnosed retinal disease in the previous 5 years between 2002 and 2010 (N = 116 388). A secondary analysis evaluated patients who had undergone photodynamic therapy (PDT) within the preceding year (N = 10 059).

METHODS: We used segmented regression analysis to evaluate changes in the rate of hospitalization for ischemic stroke associated with the introduction of bevacizumab and ranibizumab. The stroke rate was compared across 3 mutually exclusive periods: the period before the availability of bevacizumab or ranibizumab, the period of bevacizumab dominant AMD therapy, and the period of ranibizumab dominant AMD therapy.

MAIN OUTCOME MEASURES: Hospitalizations for ischemic stroke.

RESULTS: Among patients with retinal disease, neither the trend nor the level of the stroke time series changed with the uptake of bevacizumab (trend change coefficient -0.0026 stroke hospitalizations/1000 subjects/month [95% confidence interval {CI}, -0.0066 to 0.0014; P = 0.20]; level change coefficient, 0.036 stroke hospitalizations/1000 subjects [95% CI, -0.070 to 0.14; P = 0.51]), or ranibizumab (trend change coefficient: -0.0011 stroke hospitalizations/1000 subjects/month [95% CI, -0.0087 to 0.0065; P = 0.78]; level change coefficient: -0.017 stroke hospitalizations/1000 subjects [95% CI, -0.14 to 0.11; P = 0.79]). Similar results were observed in the analysis restricted to patients with recent PDT and in analyses stratified on age, sex, history of stroke, and history of diabetes.

CONCLUSIONS: The rapid uptake of vascular endothelial growth factor (VEGF) inhibitors for AMD was not associated with a change in the rate of hospitalization for stroke among Ontario seniors with retinal disease. Furthermore, stroke rates in the bevacizumab and ranibizumab periods were not different. These population-level results complement the findings of a recently published trial comparing bevacizumab and ranibizumab, and may assist clinicians and policy makers as they balance the comparative efficacy, safety, and cost of these 2 closely related treatments.

PMID: 22717458 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2012 Jun 19. doi: 10.1111/j.1755-3768.2012.02426.x. [Epub ahead of print]

Bevacizumab modulates epithelial-to-mesenchymal transition in the retinal pigment epithelial cells via connective tissue growth factor up-regulation.

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Purpose: To investigate the effect of bevacizumab treatment on connective tissue growth factor (CTGF) expression and the induction of epithelial-to-mesenchymal transition in ARPE-19 cells and human donor retinal pigment epithelium (HRPE) cells in vitro.

Methods: We quantitated the protein and gene expression level of CTGF by ELISA. The effect of Fc-Fc

receptor (Fc-FcR) interaction on CTGF expression was evaluated by CD64 siRNA silencing. Expression of epithelial-to-mesenchymal transition markers, alpha-smooth muscle actin (α-SMA) and zona occludens protein (ZO-1) was evaluated by Western blot. Cell migration and collagen gel contraction assay were examined by light microscopy, and collagen production was measured by ELISA.

Results: Bevacizumab stimulation increased CTGF expression in ARPE-19 and HRPE cells in a dose-dependent manner. CD64 gene silencing inhibited the effect of bevacizumab-induced CTGF up-regulation. Bevacizumab increased the expression of α-SMA and decreased the expression of ZO-1 in ARPE-19 cells. Bevacizumab also caused the release of type-1 collagen and increased cell migration and contraction of collagen.

Conclusions: Bevacizumab exerts pro-fibrotic effects on human RPE cells at clinical doses by up-regulation of CTGF expression via an Fc-FcR interaction. This effect of bevacizumab may be one of the underlying mechanisms involved in age-related macular degeneration therapy or intravitreal bevacizumab-associated complications.

PMID: 22712616 [PubMed - as supplied by publisher]

Ophthalmologica. 2012 Jun 15. [Epub ahead of print]

Retinal Pigment Epithelium Tears in Age-Related Macular Degeneration Treated with Antiangiogenic Drugs: A Controlled Study with Long Follow-Up.

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Purpose: To study whether anti-vascular endothelial growth factor (VEGF) therapy improves visual acuity (VA) in patients with exudative age-related macular degeneration (AMD) complicated with retinal pigment epithelium (RPE) tears.

Methods: Retrospective case-control series. Group I (control group) included 9 patients with RPE tears that received no treatment, and group II (intervention group) incorporated 12 patients treated with anti-VEGF.

Results: A statistically significant difference was found in VA between the groups from the 3rd month to the final follow-up ($p = 0.034$). Final VA improved in the treatment group ($p = 0.015$). No differences were found in central macular thickness between the groups either before or after treatment. Mean number of injections in group II was 5.75 (SD = 1.19). Most patients presented a grade 3 rip. All lesions were inactive at the end of follow-up in group II and 1 remained active in group I. The number of final atrophic/disciform scars was 6/8 in group I and 7/5 in group II.

Conclusions: RPE tears treated with antiangiogenic drugs experienced functional benefit. To the authors' knowledge, this is the first controlled series reporting effectiveness of suppression of neovascular activity with antiangiogenic treatment after RPE rip in AMD.

PMID: 22710369 [PubMed - as supplied by publisher]

J Postgrad Med. 2012 Apr;58(2):132-9.

Current trends in the pharmacotherapy of diabetic retinopathy.

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Abstract

Diabetic retinopathy (DR) is one of the most debilitating disorders of microvasculature of the retina and one of the leading causes of vision loss among the working class worldwide. At present, intravitreal anti-inflammatory (corticosteroids) and anti-angiogenesis (anti-Vascular Endothelial Growth Factor) agents are being used as wide options for the pharmacotherapy of DR and diabetic macular edema (DME). Anti-inflammatory agents (Triamcinolone acetonide and other agents) have shown evidence-based clinical benefits in various randomized clinical trials for the treatment of DR and DME, and also shown improvement in best corrected visual acuity. However, direct intravitreal injections are associated with serious side-effects like cataract and elevation of Intra Ocular Pressure. Despite this, corticosteroid therapy has been effective for DR and DME, therefore current focus is on the development of novel intravitreal steroid delivery devices that release a small quantity over a prolonged period of time. In addition to corticosteroids, anti-angiogenic agents are found to be effective for the treatment of DR and DME. The most popular target of these agents is the subfamily of proteins known as VEGF, whose over-expression is believed to play a role in numerous diseases including DR and Age-related Macular Degeneration. Intravitreal bevacizumab (Avastin®) and Ranibizumab (Lucentis®) are gaining popularity as a clinical adjunct to panretinal photocoagulation in patients with proliferative DR. Moreover, Lucentis has been recently approved by the United States Food and Drug Administration for macular edema following retinal vein occlusion. Further, systemic agents (specially, hypoglycemic, hypolipidemic and anti-hypertensive agents) have shown beneficial results in reducing the progression of DR. In conclusion, it can be stated that for the present scenario systematic use of available pharmacotherapy as an adjunct to laser photocoagulation, which is gold standard therapy, can be a useful tool in the prevention of vision loss from DR and related disorders. This article summarizes the up-to-date developments in the pharmacotherapy of DR. Method- Literature search was done on online database, Pubmed, Google Scholar, clinitrials.gov and browsing through individual ophthalmology journals and leading pharmaceutical company websites.

PMID: 22718058 [PubMed - in process]

Eye (Lond). 2012 Jun 22. doi: 10.1038/eye.2012.116. [Epub ahead of print]

Intravitreal ranibizumab for the treatment of choroidal neovascularisation secondary to angioid streaks.

Shah M, Amoaku WM.

Division of Ophthalmology and Visual Sciences, Eye and ENT Centre, University Hospital, Queen's Medical Centre, Nottingham, UK.

Aims: To assess the medium to long-term efficacy and safety of intravitreal ranibizumab for the treatment of choroidal neovascularisation (CNV) secondary to angioid streaks (AS).

Methods: A total of 12 eyes of nine patients treated with intravitreal ranibizumab (0.5 mg in 0.05 ml) for CNV secondary to AS were retrospectively identified. Efficacy of treatment was determined by changes in best-corrected LogMAR visual acuity (BCVA) and optical coherence tomography. Changes with respect to baseline BCVA were defined as improved or reduced with a gain or loss of more than 10 letters, respectively, or stable if remaining within 10 letters.

Results: Over a mean follow-up of 21.75 months (range: 1-54), patients received mean 5.75 (range: 2-15) intravitreal ranibizumab injections per affected eye. BCVA improved in three eyes (25%), stabilised in eight eyes (66.67%), and deteriorated in one eye (8.33%). There was no significant change in central retinal thickness (CRT) over the follow-up period (P=0.1072). No drug-related systemic side effects were recorded.

Conclusion: The long-term treatment of CNV secondary to AS with intravitreal ranibizumab showed a stabilisation in CRT and an improvement or stabilisation of BCVA. The absence of systemic side effects was reassuring. Further long-term prospective studies are required to validate these findings.Eye advance

online publication, 22 June 2012; doi:10.1038/eye.2012.116.

PMID: 22722486 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Invest Ophthalmol Vis Sci. 2012 Jun 19. [Epub ahead of print]

Relationship between Clinical Macular Changes and Retinal Function in Age-related Macular Degeneration.

Dimitrov PN, Robman LD, Varsamidis M, Aung KZ, Makeyeva G, Busija L, Vingrys AJ, Guymer RH.

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Purpose: To investigate the relationship between clinical macular changes and retinal function in Age-related Macular Degeneration (AMD).

Methods: 357 participants with visual acuity of better than 20/60 in the study eye were recruited, including 64 individuals with normal fundi and 293 AMD participants classified into 12 subgroups based upon the International Classification and Grading System. Visual function in the study eye was assessed using two steady-state tests (achromatic 14Hz flicker, F14Hz and isoluminant Blue color, BCT) and two adaptation measurements (Cone Photo-Stress Recovery Rate, CRR; and Rod Dark Adaptation Recovery Rate, RRR). The groups were compared on their average psychophysical measurements and ranked according to functional deficiency.

Results: Both adaptation parameters were significantly abnormal when only hard and/or intermediate drusen were evident (compared with controls, $p<0.023$) and yield considerably worse outcomes in cases with more advanced fundus changes ($p<0.001$) providing limited ability to discriminate between them (linear trend, CRR, $t=0.68$, $p=0.50$ and RRR, $t=1.76$, $p=0.08$). Steady-state measurements, however, declined gradually along the entire hierarchy of fundus changes (linear trend, F14Hz, $t=10.16$, $p<0.001$ and BCT, $t=11.19$, $p<0.001$) with flicker (14Hz) being able to detect significant functional change as early as in the intermediate drusen group, when compared to controls ($p=0.003$).

Conclusions: Steady state thresholds (14Hz Flicker and Blue Color) and clinical signs showed significant concordance across the spectrum of early AMD fundus changes. This suggests that these tests may be an effective tool for monitoring progression of AMD to supplement clinical grading.

PMID: 22714893 [PubMed - as supplied by publisher]

Soc Sci Med. 2012 May 21. [Epub ahead of print]

What do we know about the experience of age related macular degeneration? A systematic review and meta-synthesis of qualitative research.

Bennion AE, Shaw RL, Gibson JM.

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Abstract

Age Related Macular Degeneration (AMD) is the leading cause of registerable blindness with a high medical and societal cost burden. Much of the research examining experiences of living with AMD has been conducted independently with small sample sizes and has failed to impact on practice. Meta-

synthesis of qualitative research can improve the understanding of the experience of living with AMD by drawing together findings of qualitative studies. This article presents a systematic review and meta-synthesis of qualitative studies investigating the experience of AMD (literature searched up to April 2012; published studies identified range from 1996 to 2009). The review highlights themes relating to: functional limitations, adaptation and independence; feelings about the future with vision impairment; interaction with the health service; social engagement; disclosure; and the emotional impacts of living with AMD. Attention to the experience of living with AMD can help us to better understand the needs of patients. This meta-synthesis aimed to bring together the findings of qualitative research studies and highlights important areas for consideration when caring for patients with AMD. Our findings suggest that a holistic approach to service provision and support for AMD is needed which takes into account individuals' needs and experiences when coping with and adjusting to living with AMD. This support should aim to reduce stigma, increase social engagement, and develop the psychological resources of patients with AMD.

PMID: 22709445 [PubMed - as supplied by publisher]

Am J Prev Med. 2012 Jul;43(1):48-54.

Diabetic retinopathy and age-related macular degeneration in the U.S.

Gibson DM.

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BACKGROUND: Diabetic retinopathy and age-related macular degeneration (AMD) are two of the most common eye diseases in the U.S. Effective treatments exist for some stages of these conditions.

PURPOSE: This goal of this study was to examine the frequency and predictors of unawareness of diabetic retinopathy and AMD.

METHODS: The 2005-2008 National Health and Nutrition Examination Survey (NHANES) collected digital retinal images of survey participants aged ≥40 years that were graded for diabetic retinopathy and AMD using standard protocols. A sample of individuals with diabetic retinopathy was created, as was a separate sample of individuals with AMD. Individuals were categorized as unaware of their condition if they did not report that they had the condition. Separate logistic regression models of unawareness of diabetic retinopathy and AMD were estimated in 2011.

RESULTS: This study estimated that 73% of individuals with diabetic retinopathy and 84% of individuals with AMD were unaware of their condition. The odds of unawareness of diabetic retinopathy were higher for individuals with less-severe diabetic retinopathy, shorter diabetes duration, smaller families, or who had not had a recent eye exam. The odds of unawareness of AMD were higher for individuals with "early" AMD or who were younger, less educated, or not primarily English speakers.

CONCLUSIONS: The very high frequency of unawareness of diabetic retinopathy and AMD suggests that unawareness of these conditions should be a major public health concern and that efforts are needed to increase the frequency of eye exams among those at risk for these conditions.

PMID: 22704745 [PubMed - in process]

Ophthalmology. 2012 Jun 15. [Epub ahead of print]

Cognitive Impairment in Age-related Macular Degeneration and Geographic Atrophy.

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Department of Ophthalmology, Seoul National University College of Medicine, Seoul, Korea.

PURPOSE: To investigate cognitive function in patients with early and late age-related macular degeneration (AMD) compared with an elderly, community-dwelling Korean population without AMD.

DESIGN: Case-control study.

PARTICIPANTS: We enrolled 170 AMD patients and 190 non-AMD community-based controls.

METHODS: A comprehensive battery for cognitive function evaluation consisting of 15 psychological tests, including a depression evaluation test, was used. Cognitive function scores were adjusted for age, gender, education, and visual acuity (VA). We categorized AMD as early AMD, exudative AMD, or geographic atrophy.

MAIN OUTCOME MEASURES: The primary outcome measure was the degree of cognitive impairment, as assessed by the Korean versions of the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Assessment Battery, Benton Visual Retention Test, and Digit Span Test Forward and Backward.

RESULTS: Patients with AMD showed lower global cognition scores than did normal controls (mean Mini-Mental State Examination [MMSE] score, 24.97 vs 25.99; P<0.001). Among cognitive functions, visuospatial function, verbal memory, visual memory, and frontal function were impaired in AMD patients relative to normal controls. The rate of mild cognitive impairment (MCI) was higher in AMD patients than in controls (52.4% vs 26.8%; P<0.001), with an odds ratio (OR) of 3.127 (95% confidence interval, 1.855-5.271) after adjustment for age, education, and VA. Geographic atrophy was associated with the highest risk of MCI (OR, 4.431; 95% confidence interval, 1.413-13.898) and a clinically significant reduction in MMSE scores (23.42) relative to the controls. There was a trend of worsening cognitive function test scores from the controls to the early AMD, then the exudative AMD, and finally the geographic atrophy patients, after adjustment for covariates. AMD patients with poor VA (≤20/100) had 6 times the risk of MCI as AMD patients with good or moderate VA (>20/100).

CONCLUSIONS: Patients with AMD, especially those with the geographic atrophy subtype, are at greater risk for cognitive impairment than are non-AMD control subjects. In the visual rehabilitation of AMD patients, potential cognitive impairment should be taken into consideration.

PMID: 22705343 [PubMed - as supplied by publisher]

Hum Gene Ther. 2012 Jun 20. [Epub ahead of print]

Safety and Biodistribution of an EIAV-based Gene Therapy, RetinoStat®, for Age-related Macular Degeneration.

Binley K, Widdowson PS, Kelleher M, de Belin J, Loader J, Ferrige G, Leroux-Carlucci MA, Esapa M, Chipchase D, Angell-Manning D, Ellis S, Mitrophanous K, Miskin JE, Bantseev V, Nork TM, Miller P, Naylor S.

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Abstract

RetinoStat® is an EIAV-based lentiviral gene therapy vector that expresses the angiostatic proteins endostatin and angiostatin that is delivered via a subretinal injection for the treatment of the wet-form of age -related macular degeneration (AMD). We initiated six month safety and biodistribution studies in two species; Rhesus macaques and Dutch-belted rabbits. Following subretinal administration of RetinoStat® the level of human endostatin and angiostatin proteins in the vitreous of the treated eyes peaked at ~1 month after dosing and remained high for the duration of the study. Regular ocular exams revealed a mild

to moderate transient ocular inflammation that resolved within 1 month of dosing in both species. There were no significant long-term changes in the electroretinograms or intraocular pressure measurements in either rabbits or macaques post-dosing compared to the baseline reading in RetinoStat® treated eyes. Histological evaluation did not reveal any structural changes in the eye although there was an infiltration of mononuclear cells in the vitreous, retina and choroid. No antibodies to any of the RetinoStat® vector components including the transgenes could be detected in the serum from either species and biodistribution analysis demonstrated that the RetinoStat® vector was maintained within the ocular compartment. In summary, these studies found RetinoStat® to be well-tolerated, localised and capable of persistent expression following subretinal delivery.

PMID: 22716662 [PubMed - as supplied by publisher]

Pathogenesis

PLoS One. 2012;7(6):e38616. Epub 2012 Jun 8.

X-box binding protein 1 is essential for the anti-oxidant defense and cell survival in the retinal pigment epithelium.

Zhong Y, Li J, Wang JJ, Chen C, Tran JT, Saadi A, Yu Q, Le YZ, Mandal MN, Anderson RE, Zhang SX.

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Abstract

Damage to the retinal pigment epithelium (RPE) is an early event in the pathogenesis of age-related macular degeneration (AMD). X-box binding protein 1 (XBP1) is a key transcription factor that regulates endoplasmic reticulum (ER) homeostasis and cell survival. This study aimed to delineate the role of endogenous XBP1 in the RPE. Our results show that in a rat model of light-induced retinal degeneration, XBP1 activation was suppressed in the RPE/choroid complex, accompanied by decreased anti-oxidant genes and increased oxidative stress. Knockdown of XBP1 by siRNA resulted in reduced expression of SOD1, SOD2, catalase, and glutathione synthase and sensitized RPE cells to oxidative damage. Using Cre/LoxP system, we generated a mouse line that lacks XBP1 only in RPE cells. Compared to wildtype littermates, RPE-XBP1 KO mice expressed less SOD1, SOD2, and catalase in the RPE, and had increased oxidative stress. At age 3 months and older, these mice exhibited apoptosis of RPE cells, decreased number of cone photoreceptors, shortened photoreceptor outer segment, reduced ONL thickness, and deficit in retinal function. Electron microscopy showed abnormal ultrastructure, Bruch's membrane thickening, and disrupted basal membrane infolding in XBP1-deficient RPE. These results indicate that XBP1 is an important gene involved in regulation of the anti-oxidant defense in the RPE, and that impaired activation of XBP1 may contribute to RPE dysfunction and cell death during retinal degeneration and AMD.

PMID: 22715395 [PubMed - in process] PMCID: PMC3371004

Proteomics. 2012 Jun 18. doi: 10.1002/pmic.201100668. [Epub ahead of print]

Human and rat brain lipofuscin proteome.

Ottis P, Koppe K, Onisko B, Dynin I, Arzberger T, Kretzschmar H, Requena JR, Silva CJ, Huston JP, Korth C.

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Abstract

The accumulation of an autofluorescent pigment called lipofuscin in neurons is an invariable hallmark of brain aging. So far, this material has been considered to be waste material without particular relevance for cellular pathology. However, two lines of evidence argue that lipofuscin may play a yet unidentified role for pathological cellular functions: 1. Genetic forms of premature accumulation of similar autofluorescent material in neuronal ceroid lipofuscinosis indicate a direct disease-associated link to lipofuscin, 2. Retinal pigment epithelium cell lipofuscin is mechanistically linked to age-associated macular degeneration. Here, we purified autofluorescent material from the temporal and hippocampal cortices of three different human individuals by a two-step ultracentrifugation on sucrose gradients. For human brain lipofuscin, we could identify a common denominator of 49 (among > 200 total) proteins that are mainly derived from mitochondria, cytoskeleton and cell membrane. This brain lipofuscin proteome was validated in an interspecies comparison with whole brain rat lipofuscin (total > 300 proteins), purified by the same procedure, yielding an overlap of 32 proteins (64%) between lipofuscins of both species. Our study is the first to characterize human and rat brain lipofuscin and identifies high homology, pointing to similar cellular pathomechanisms of age-associated lipofuscin accumulation despite the huge (40 fold) difference in the lifespan of both species for neuronal lipofuscin accumulation. Our identification of these distinct proteins will now allow research in age-associated dysfunctional molecular pathways during dysfunctional lysosomal degradation.

PMID: 22707227 [PubMed - as supplied by publisher]

J Proteome Res. 2012 Jun 15. [Epub ahead of print]

Proteomic Analysis of the Aqueous Humor in Age-related Macular Degeneration (AMD) Patients.

Kim TW, Kang JW, Ahn J, Lee EK, Cho KC, Han BN, Hong NY, Park J, Kim KP.

Abstract

Age-related macular degeneration (AMD) can lead to an irreversible loss of central vision among the elderly. Although a large number of growth factor pathways, including the vascular endothelial growth factor (VEGF), have been implicated in the pathogenesis, no study has been directed towards assessing the whole proteomic composition in the aqueous humor (AH) among AMD patients. The AH contains proteins secreted from the anterior segment tissues, and these proteins may play an important role in the pathogenesis of AMD. Thus, comparisons between the proteomic profiles of the AH between AMD patients and non-AMD controls can lead to the verification of novel pathogenic proteins used as potential clinical biomarkers. In this study, we used discovery-based proteomics and Multiple Reaction Monitoring Mass Spectrometry (MRM-MS). The AH from patients with AMD were analyzed and compared with the AH from patients who had cataract surgery. A total of 154 proteins with at least two unique peptides were identified in the AH. Of these 154 proteins identified by discovery-based proteomics, 10 AH proteins were novel identifications. The protein composition in AH was different between AMD patients and non-AMD controls. Subsequently, a systematic MRM-MS assay was performed in seven highly abundant differentially expressed proteins from these groups. Differential expression of three proteins was observed in the AH among AMD patients compared with the AH among cataract controls ($p<0.0312$). Elucidation of the aqueous proteome will establish a foundation for protein function analysis and identify differentially expressed markers associated with AMD. This study demonstrates that integrated proteomic technologies can yield novel biomarkers to detect exudative AMD.

PMID: 22702841 [PubMed - as supplied by publisher]

Mol Aspects Med. 2012 Jun 13. [Epub ahead of print]

Animal Models of Age Related Macular Degeneration.

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Abstract

Age related macular degeneration (AMD) is the leading cause of vision loss of those over the age of 65 in the industrialized world. The prevalence and need to develop effective treatments for AMD has lead to the development of multiple animal models. AMD is a complex and heterogeneous disease that involves the interaction of both genetic and environmental factors with the unique anatomy of the human macula. Models in mice, rats, rabbits, pigs and non-human primates have recreated many of the histological features of AMD and provided much insight into the underlying pathological mechanisms of this disease. In spite of the large number of models developed, no one model yet recapitulates all of the features of human AMD. However, these models have helped reveal the roles of chronic oxidative damage, inflammation and immune dysregulation, and lipid metabolism in the development of AMD. Models for induced choroidal neovascularization have served as the backbone for testing new therapies. This article will review the diversity of animal models that exist for AMD as well as their strengths and limitations.

PMID: 22705444 [PubMed - as supplied by publisher]

Prog Retin Eye Res. 2012 Jun 18. [Epub ahead of print]

Novel roles for α-crystallins in retinal function and disease.

Kannan R, Sreekumar PG, Hinton DR.

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Abstract

α-Crystallins are key members of the superfamily of small heat shock proteins that have been studied in detail in the ocular lens. Recently, novel functions for α-crystallins have been identified in the retina and in the retinal pigmented epithelium (RPE). αB-Crystallin has been localized to multiple compartments and organelles including mitochondria, golgi apparatus, endoplasmic reticulum and nucleus. α-Crystallins are regulated by oxidative and endoplasmic reticulum stress, and inhibit apoptosis-induced cell death. α-Crystallins interact with a large number of proteins that include other crystallins, and apoptotic, cytoskeletal, inflammatory, signaling, angiogenic, and growth factor molecules. Studies with RPE from αB-crystallin deficient mice have shown that αB-crystallin supports retinal and choroidal angiogenesis through its interaction with vascular endothelial growth factor. αB-Crystallin has also been shown to have novel functions in the extracellular space. In RPE, αB-crystallin is released from the apical surface in exosomes where it accumulates in the interphotoreceptor matrix and may function to protect neighboring cells. In other systems administration of exogenous recombinant αB-crystallin has been shown to be anti-inflammatory. Another newly described function of αB-crystallin is its ability to inhibit β-amyloid fibril formation. α-Crystallin mini-chaperone peptides have been identified that elicit anti-apoptotic function in addition to being efficient chaperones. Generation of liposomal particles and other modes of nanoencapsulation of these minipeptides could offer great therapeutic advantage in ocular delivery for a wide variety of retinal degenerative, inflammatory and vascular diseases including age related macular degeneration and diabetic retinopathy.

PMID: 22721717 [PubMed - as supplied by publisher]

Epidemiology

Eur J Epidemiol. 2012 Jun 19. [Epub ahead of print]

Evidence for a considerable decrease in total and cause-specific incidences of blindness in Germany.

Claessen H, Genz J, Bertram B, Trautner C, Giani G, Zöllner I, Icks A.

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Abstract

The objectives of this study are to estimate the recent population-based incidences of all-cause and cause-specific blindness in Germany and compare them with results from a similar study conducted in 1994-1998. All blindness allowance recipients newly registered between January 2008 and December 2009 in a region in southern Germany (population, approximately 3.5 million) were assessed and their ophthalmological reports reviewed. The main causes of blindness were identified and their incidences estimated. There were 572 newly registered cases of blindness allowance. The all-cause incidence of blindness (per 100,000 person-years) in the general population was 8.4 (95 % confidence interval, 7.8-9.2), and the highest incidences were for macular degeneration (3.4; 3.0-3.9), diabetic retinopathy (0.8; 0.6-1.1) and glaucoma (0.7; 0.5-0.9). During the last two decades, blindness incidences decreased for all the main causes (standardised to the West German population 1991: 12.3; 11.9-12.7 in 1994-1998 vs. 7.3; 6.7-8.0 in 2008-2009). The highest absolute decrease was for macular degeneration and the highest relative decrease was for cataract. The most frequent main causes of blindness in Germany remained macular degeneration, diabetic retinopathy and glaucoma. Our findings suggest a remarkable decrease in the incidences of blindness, probably because of new diagnostic options and effective treatments.

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Genetics

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Heritability and Genome-Wide Association Study to Assess Genetic Differences between Advanced Age-Related Macular Degeneration Subtypes.

Sobrin L, Ripke S, Yu Y, Fagerness J, Bhangale TR, Tan PL, Souied EH, Buitendijk GH, Merriam JE, Richardson AJ, Raychaudhuri S, Reynolds R, Chin KA, Lee AY, Leveziel N, Zack DJ, Campochiaro P, Smith RT, Barile GR, Hogg RE, Chakravarthy U, Behrens TW, Uitterlinden AG, van Duijn CM, Vingerling JR, Brantley MA Jr, Baird PN, Klaver CC, Allikmets R, Katsanis N, Graham RR, Ioannidis JP, Daly MJ, Seddon JM.

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PURPOSE: To investigate whether the 2 subtypes of advanced age-related macular degeneration (AMD), choroidal neovascularization (CNV), and geographic atrophy (GA) segregate separately in families and to identify which genetic variants are associated with these 2 subtypes.

DESIGN: Sibling correlation study and genome-wide association study (GWAS).

PARTICIPANTS: For the sibling correlation study, 209 sibling pairs with advanced AMD were included. For the GWAS, 2594 participants with advanced AMD subtypes and 4134 controls were included. Replication

cohorts included 5383 advanced AMD participants and 15 240 controls.

METHODS: Participants had the AMD grade assigned based on fundus photography, examination, or both. To determine heritability of advanced AMD subtypes, a sibling correlation study was performed. For the GWAS, genome-wide genotyping was conducted and 6 036 699 single nucleotide polymorphisms (SNPs) were imputed. Then, the SNPs were analyzed with a generalized linear model controlling for genotyping platform and genetic ancestry. The most significant associations were evaluated in independent cohorts.

MAIN OUTCOME MEASURES: Concordance of advanced AMD subtypes in sibling pairs and associations between SNPs with GA and CNV advanced AMD subtypes.

RESULTS: The difference between the observed and expected proportion of siblings concordant for the same subtype of advanced AMD was different to a statistically significant degree (P = 4.2×10(-5)), meaning that in siblings of probands with CNV or GA, the same advanced subtype is more likely to develop. In the analysis comparing participants with CNV to those with GA, a statistically significant association was observed at the ARMS2/HTRA1 locus (rs10490924; odds ratio [OR], 1.47; P = 4.3×10(-9)), which was confirmed in the replication samples (OR, 1.38; P = 7.4×10(-14) for combined discovery and replication analysis).

CONCLUSIONS: Whether CNV versus GA develops in a patient with AMD is determined in part by genetic variation. In this large GWAS meta-analysis and replication analysis, the ARMS2/HTRA1 locus confers increased risk for both advanced AMD subtypes, but imparts greater risk for CNV than for GA. This locus explains a small proportion of the excess sibling correlation for advanced AMD subtype. Other loci were detected with suggestive associations that differ for advanced AMD subtypes and deserve follow-up in additional studies.

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Rapid detection of CFH (p.Y402H) and ARMS2 (p.A69S) polymorphisms in age-related macular degeneration using high-resolution melting analysis.

Mello E, Falsini B, Zuppi C, Giardina B, Concolino P, Capoluongo E.

Background: Age-related macular degeneration (AMD) is a complex disorder causing irreversible central vision loss. Complement Factor H (CFH) and age-related maculopathy susceptibility 2 (ARMS2) are now widely accepted as important AMD susceptibility genes. In particular, two specific variants, CFH p.Y402H and ARMS2 p.A69S, have been reported as strongly AMD associated. In order to perform the genetic screening of these single nucleotide polymorphisms (SNPs), we describe a high resolution melting analysis (HRM) as a rapid closed tube mutation scanning assay.

Methods: To validate HRM genotyping, 94 DNA samples from AMD patients (previously genotyped by sequence analysis) were analyzed. PCR amplification and melting curve analysis were performed in the LightCycler 480 Real-Time PCR System. In order to evaluate the accuracy of the HRM assay, we performed a blinded study of 20 unknown independent samples.

Results: We correctly genotyped all samples. In fact, all samples corresponded to the previous genotype assignments.

Conclusions: Early identification of individuals with genetic risk variants CFH p.Y402H and ARMS2 p.A69S is clinically important for the definition of AMD status. High-resolution DNA melting is homogenous, accurate and rapid method for CFH and ARMS2 genotyping.

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Study of FTMT and ABCA4 genes in a patient affected by age-related macular degeneration: identification and analysis of new mutations.

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Background: Age-related macular degeneration (AMD) is a multifactorial disease for which an involvement of alterations in the retinal ABC transporter gene (ABCA4) is still debated. Oxidative stress in retinal pigment epithelial cells has been postulated to contribute to the pathogenesis of the disease. Mitochondrial ferritin (FtMt), an iron-sequestering protein, is expressed in cell types characterized by high metabolic activity and oxygen consumption, including human retina, suggesting a role in protecting mitochondria from iron-dependent oxidative damage. Based on these findings we wanted to investigate whether mutations in this gene could be found in AMD patients.

Methods: Mutational scanning of the FTMTgene was performed in a cohort of 50 patients affected by age-related macular degeneration. The ABCA4 gene was also scanned in one patient carrying an FtMt mutation. In silico analyses were carried out on the identified variants. The recombinant form of FtMt variant was expressed in Escherichia coli and biochemically characterized.

Results: One patient was found to be heterozygous for two previously unreported genetic changes: a complex FtMt mutation (c.437_450delinsCT: delAGGACATCAAGAAGinsCT) and a missense p.Leu973Phe (c.2919G>T) mutation in exon 20 of ABCA4. Computational analyses predicted a severe structural impairment for FtMt variant and a mild destabilizing effect for ABCA4. E. coli expression of recombinant FtMt variant yielded a highly insoluble protein that could not be renatured under in vitro conditions suitable for wild-type ferritins.

Conclusions: Our findings suggest that the FtMt mutation may determine a condition similar to haploinsufficiency resulting in a reduced protection from iron-dependent oxidative stress in mitochondria.

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The investigation of allele and genotype frequencies of human C3 (rs2230199) in south Iranian population.

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Abstract

The complement system is an important mediator of natural and acquired immunity. The complement system genes coding complement proteins have polymorphisms. Hereditary deficiencies of this system predispose to autoimmune conditions such as age-dependent macular degeneration or impairment of immunity against microorganisms. When different populations are compared, the frequency of complement polymorphism shows a very marked geographical distribution. The frequency of the functional polymorphism rs2230199 (Arg80Gly; C > G) in the C3 gene was determined in population from south of Iran (n = 200), using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). One hundred thirty-eight persons (69 %) were homozygous for C allele (CC or SS); fifty-six person (28 %) heterozygote GC (FS) and six people were homozygous for G allele (GG or FF) (3 %). The allele frequency was 82 % for C3S and 18 % for C3F. A distribution of C3C allele frequency in our population is different from the reports of Asians (100 %); Indians (90-98 %); African-American (93 %); Africans (99 %) and south Brazilian (97 %). However, this finding is similar with the findings Caucasian (80-82 %) (http://

www.ncbi.nlm.nih.gov/SNP); Americans (80 %); Pushtoon, Hazaras, Osbek and Tajik ethnic groups in Afghanistan (88-90 %) and Tunisian population (84 %). Our study confirmed significant inter-ethnic differences in C3 (rs2230199) frequencies between south Iranians and other ethnic groups. The analysis of genetic variation in complement genes is a tool to provide new insights into the evolution of the human immune system.

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Diet

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Microbial carotenoids.

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Abstract

Carotenoids are among the most widely distributed pigments in nature, and they are exclusively synthesized by plants and microorganisms. These compounds may serve a protective role against many chronic diseases such as cancers, age-related macular degeneration, and cardiovascular diseases and also act as an excellent antioxidant system within cells. Recent advances in the microbial genome sequences and increased understanding about the genes involved in the carotenoid biosynthetic pathways will assist industrial microbiologists in their exploration of novel microbial carotenoid production strategies. Here we present an overview of microbial carotenogenesis from biochemical, proteomic, and biotechnological points of view.

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