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MD Research News

Issue 22

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Drug Treatment

Proc Natl Acad Sci U S A. 2011 Mar 28. [Epub ahead of print]

Ciliary neurotrophic factor delivered by encapsulated cell intraocular implants for treatment of geographic atrophy in age-related macular degeneration.

Zhang K, Hopkins JJ, Heier JS, Birch DG, Halperin LS, Albini TA, Brown DM, Jaffe GJ, Tao W, Williams GA.

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Abstract

There is no treatment available for vision loss associated with advanced dry age-related macular degeneration (AMD) or geographic atrophy (GA). In a pilot, proof of concept phase 2 study, we evaluated ciliary neurotrophic factor (CNTF) delivered via an intraocular encapsulated cell technology implant for the treatment of GA. We designed a multicenter, 1-y, double-masked, sham-controlled dose-ranging study. Patients with GA were randomly assigned to receive a high-or low-dose implant or sham surgery. The primary endpoint was the change in best corrected visual acuity (BCVA) at 12 mo. CNTF treatment resulted in a dose-dependent increase in retinal thickness. This change was followed by visual acuity stabilization (loss of less than 15 letters) in the high-dose group (96.3%) compared with low-dose (83.3%) and sham (75%) group. A subgroup analysis of those with baseline BCVA at 20/63 or better revealed that 100% of patients in the high-dose group lost <15 letters compared with 55.6% in the combined low-dose/sham group (P = 0.033). There was a 0.8 mean letter gain in the high-dose group compared with a 9.7 mean letter loss in the combined low-dose/sham group (P = 0.0315). Both the implant and the implant procedure were well-tolerated. These findings suggest that CNTF delivered by the encapsulated cell technology implant appears to slow the progression of vision loss in GA, especially in eyes with 20/63 or better vision at baseline.

PMID: 21444807 [PubMed - as supplied by publisher]

Curr Diabetes Rev. 2011 Mar 24. [Epub ahead of print]

Intravitreal Anti VEGF Drugs as Adjuvant Therapy in Diabetic Retinopathy Surgery.

Montero JA, Ruiz-Moreno JM, Correa ME.

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Abstract

The use of intravitreal anti vascular endothelial growth factor (anti-VEGF) drugs such as pegaptanib, ranibizumab and bevacizumab has been widely reported to treat complications such as macular edema and rubeosis. During the past few years they have also been used as an adjuvant therapy to reduce intraocular bleeding during vitrectomy in eyes with proliferative diabetic retinopathy as well as to reduce the occurrence of vitreous haemorrhages in vitrectomized eyes and facilitate glaucoma surgery. In this paper we review the use of anti VEGF drugs in the surgical management of diabetic retinopathy related complications.

PMID: 21438852 [PubMed - as supplied by publisher]

Eye (Lond). 2011 Apr 1. [Epub ahead of print]

Preclinical aspects of anti-VEGF agents for the treatment of wet AMD: ranibizumab and bevacizumab.

Meyer CH, Holz FG.

Department of Ophthalmology, University of Bonn, Bonn, Germany.

Abstract

Three anti-vascular endothelial growth factor (VEGF) therapies are currently used for the treatment of patients with wet age-related macular degeneration (AMD): pegaptanib, ranibizumab, and bevacizumab. Ranibizumab is an antibody fragment approved for the treatment of wet AMD. Bevacizumab is a full-length antibody registered for use in oncology but unlicensed for wet AMD. However, it is used off-label worldwide not only for wet AMD but also for various other ocular diseases associated with macular edema and abnormal vessel growth. We consider aspects of ranibizumab and bevacizumab in relation to their molecular characteristics, in vitro and in vivo properties, and preclinical safety data. Before 2009, most studies described the short-term toxicity of bevacizumab in multiple cell types of the eye. Since 2009, an increasing number of studies have compared the properties of ranibizumab and bevacizumab and investigated their impact on retinal cell functioning. Compared with bevacizumab, ranibizumab neutralizes VEGF better at low concentrations, maintains efficacy for longer, and has a higher retinal penetration and potency. Studies in animals demonstrate ranibizumab to be better localized to the injected eye, whereas bevacizumab appears to have a greater effect in the fellow eye. In humans, a localized and systemic effect has been reported for both molecules. In conclusion, overlapping yet distinct pharmacological properties of ranibizumab and bevacizumab indicate that safety or efficacy data from one cannot be extrapolated to the other.Eye advance online publication, 1 April 2011; doi:10.1038/eye.2011.66.

PMID: 21455242 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Rev Med Suisse. 2011 Feb 2;7(280):322-3.

[Dry macular degeneration and embryonic stem cells].

[Article in French]

Nau JY.

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PMID: 21381277 [PubMed - indexed for MEDLINE]

Nat Neurosci. 2011 Mar 27. [Epub ahead of print]

Large-scale remapping of visual cortex is absent in adult humans with macular degeneration.

Baseler HA, Gouws A, Haak KV, Racey C, Crossland MD, Tufail A, Rubin GS, Cornelissen FW, Morland AB.

York Neuroimaging Centre, Department of Psychology, University of York, York, UK.

Abstract

The occipital lobe contains retinotopic representations of the visual field. The representation of the central retina in early visual areas (V1-3) is found at the occipital pole. When the central retina is lesioned in both eyes by macular degeneration, this region of visual cortex at the occipital pole is accordingly deprived of input. However, even when such lesions occur in adulthood, some visually driven activity in and around the occipital pole can be observed. It has been suggested that this activity is a result of remapping of this area so that it now responds to inputs from intact, peripheral retina. We evaluated whether or not remapping of visual cortex underlies this activity. Our functional magnetic resonance imaging results provide no evidence of remapping, questioning the contemporary view that early visual areas of the adult human brain have the capacity to reorganize extensively.

PMID: 21441924 [PubMed - as supplied by publisher]

Prog Retin Eye Res. 2011 Mar 24. [Epub ahead of print]

Parallel findings in Age-related Macular Degeneration and Alzheimer's Disease.

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Department of Ophthalmology and Visual Science, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8510, Japan.

PMID: 21440663 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2011 Mar 30. [Epub ahead of print]

Incorrect study design and analysis: effect of isometric exercise on choroidal blood flow in patients with age-related macular degeneration.

McGwin G Jr.

University of Alabama at Birmingham, Birmingham, Alabama, USA.

PMID: 21450756 [PubMed - as supplied by publisher]

Epidemiology & pathogenesis

Invest Ophthalmol Vis Sci. 2011 Mar 29. [Epub ahead of print]

Incidence of blindness and severe visual impairment in Germany - projections for 2030.

Finger RP, Fimmers R, Holz FG, Scholl HP.

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Background: Estimates for the incidence of severe visual impairment and blindness (SVI/B) and their

causes are key to good health service planning. Thus the database of Germany's largest state's blind registry was used to estimate current incidence rates, and to project incidence rates (IR) for Germany to 2010 and 2030.

Methods: The sample consisted of 3328 blind/severely visually impaired newly registered between 2000-2008. According to German law, SVI and B was defined as visual acuity equal or below 20/1000 and 20/4000, respectively, in the better seeing eye. Data of the reference population were stratified by age and gender and used to estimate current IRs. Standardized IRs were estimated for Germany for 2010 and 2030 using national demographic projections.

Results: Age-related macular degeneration (AMD) accounted for 50% of all incidence of SVI/B (5.56/100,000 personyears (PY), followed by glaucoma (15%; 1.65/100,000PY) and diabetic eye disease (10%; 1.16/100,000PY). All current IRs will rise until 2030, with the most pronounced increase in AMD. By 2030 a national AMD IR of 9.5/100,000 PY is expected, accounting for 57% of all incidence of SVI/B in Germany. The incidence of SVI/B in women will be more than twofold compared to men in 2030 (9187 versus 3716 incident cases in 2030).

Conclusions: There will be a dramatic increase of SVI/B until 2030 in Germany leading to a substantial increase in the need for health and social service provision, with a focus on visually impaired elderly women.

PMID: 21447690 [PubMed - as supplied by publisher]

Surv Ophthalmol. 2011 Mar 24. [Epub ahead of print]

Lipids and Age-Related Macular Degeneration.

Kishan AU, Modjtahedi BS, Martins EN, Modjtahedi SP, Morse LS.

Harvard Medical School, Boston, MA, USA.

Abstract

Given the considerable public health burden imposed by age-related macular degeneration (AMD), much effort has been directed towards elucidating principles of pathogenesis in order to identify risk factors and develop preventive measures and treatments. Together with epidemiological evidence linking cardiovascular risk factors with AMD risk and basic science work examining the role of lipid metabolism in AMD, numerous human studies have assayed a potential relationship between dietary lipids and the development of AMD. We examine the evidence for a role for lipid metabolism in AMD, highlighting key basic biochemical principles, work in animal models, and relevant human studies. The topics of lipoprotein modulation and omega-3 fatty acid intake receive special attention from both a basic science and clinical study standpoint. The evidence suggests that consumption of omega-3 fatty acids, perhaps in concert with antioxidants, may constitute a rational preventative strategy against AMD development, though, absent an appropriately developed double-blind, randomized control trial, insufficient data exist to recommend implementation in the clinical setting at this time.

PMID: 21439604 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2011 Mar 29. [Epub ahead of print]

Pneumatic displacement of submacular hemorrhage with or without tissue plasminogen activator.

Mizutani T, Yasukawa T, Ito Y, Takase A, Hirano Y, Yoshida M, Ogura Y.

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PURPOSE: To assess the efficacy and complications of intravitreal injection of sulfur hexafluoride (SF(6)) gas with/without tissue plasminogen activator (tPA) for displacing submacular hemorrhage.

METHODS: The medical records of 53 eyes that underwent pneumatic displacement for submacular hemorrhage were reviewed retrospectively. Submacular hemorrhage was related to exudative age-related macular degeneration (AMD) in 39 eyes and ruptured retinal arterial macroaneurysms in 14 eyes, and treated with intravitreal injection of SF(6) gas with or without tPA.

RESULTS: Compared with preoperatively (mean follow-up, 18.4 months), the final visual acuity (VA) improved by 0.3 or more logMAR unit in 34 eyes (64.2%), stabilized within 0.3 logMAR in 15 eyes (28.3%), and deteriorated in four eyes (7.5%). In eyes with AMD, hemorrhage including vitreous hemorrhage recurred in eight (22.2%) of 36 eyes treated with tPA and one (33.3%) of three eyes not treated with tPA. In eyes with macroaneurysms, hemorrhage recurred in four (100%) of four eyes treated with tPA and in one (10.0%) of ten eyes without tPA ($p < 0.005$). Eight eyes underwent vitrectomy for recurrent hemorrhage. During follow-up, photodynamic therapy or intravitreal ranibizumab or pegaptanib was administered in 16 (41.0%) of 39 eyes with AMD. Postoperative ocular hypertension persisting over 3 days was not observed.

CONCLUSIONS: Intravitreal SF(6) gas plus tPA may be well-accepted, with good visual outcomes and no remarkable complications for treating submacular hemorrhage secondary to AMD. tPA is not recommended for ruptured retinal arterial macroaneurysms, because of a higher incidence of subsequent vitreous hemorrhage. Pneumatic displacement of submacular hemorrhage without tPA may provide good visual outcomes with less re-bleeding.

PMID: 21445629 [PubMed - as supplied by publisher]

Ophthalmology. 2011 Mar 26. [Epub ahead of print]

Prevalence of Age-Related Macular Degeneration in a Rural Chinese Population: The Handan Eye Study.

Yang K, Liang YB, Gao LQ, Peng Y, Shen R, Duan XR, Friedman DS, Sun LP, Mitchell P, Wang NL, Wong TY, Wang JJ.

Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing Ophthalmology and Visual Science Key Lab, Beijing, China.

PURPOSE: To describe the prevalence of age-related degeneration (AMD) in a rural Chinese population and to assess its associations with age, gender, and smoking.

DESIGN: Population-based cross-sectional.

PARTICIPANTS: Persons aged 30+ years, recruited between October 2006 and October 2007, from Yongnian County, Handan, Hebei Province, China.

METHODS: All participants underwent a standardized interview and comprehensive eye examinations, including digital retinal photography of both eyes. Trained graders assessed the presence and severity of AMD lesions following the modified Wisconsin Age-related Maculopathy Grading System (WARMGS) used in the Blue Mountains Eye Study (BMES). Direct age standardization to the world population (year 2000) was performed to compare the prevalence across different populations.

MAIN OUTCOME MEASURES: AMD and WARMGS.

RESULTS: Of 6830 participates, fundus photographs were gradable for 6581 persons (96.4%), including 4049 aged 50+ years. Early and late AMD prevalence rates were 3.0% and 0.1%, respectively, among participants. The age-standardized prevalence rates among participants aged 50+ years were 4.7% and 0.2%, respectively. After controlling for age, men had a higher prevalence of early (3.9% vs. 2.3%, odds ratio [OR] 1.7; 95% confidence interval [CI], 1.3-2.2) and late AMD (0.1% vs. 0.03%; OR 3.5; CI, 0.4-33.4)

compared with women. Older age (sex-adjusted OR 1.7; CI, 1.3-2.2 per decade of age) and current smoking (age-sex-adjusted OR 1.4; CI, 1.0-2.1) were significantly associated with early AMD prevalence. The proportion of current smokers was substantially higher in men (58.7%) than in women (0.3%). The attributable risk of early AMD from smoking among Chinese men was 24.2%. After controlling for current smoking, the excess prevalence of early AMD in men compared with women reduced by 50% (OR 1.4; 95% CI, 0.9-2.0).

CONCLUSIONS: The prevalence of early AMD in this rural Chinese sample was similar to white persons in the BMES and Asian Malays in the Singapore Malay Eye Study. Late AMD prevalence, however, was lower. Higher prevalence rates for early and late AMD in men compared with women were largely attributed to substantially higher proportions of smokers in rural Chinese men than in women.

PMID: 21444116 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2011 Mar 29. [Epub ahead of print]

MCP-1-activated monocytes induce apoptosis in human retinal pigment epithelium.

Yang D, Elner SG, Chen X, Field MG, Petty HR, Elner VM.

Departments of Ophthalmology and Visual Sciences.

Purpose: The inflammatory response in age-related macular degeneration (AMD) is characterized by mononuclear leukocyte infiltration of the outer blood-retina barrier formed by the retinal pigment epithelium (RPE). A key mechanistic element in AMD progression is RPE dysfunction and apoptotic cell loss. The purpose of this study was to evaluate whether monocyte chemoattractant protein-1 (MCP-1)-activated monocytes induce human RPE apoptosis and whether Ca(2+) and reactive oxygen species (ROS) are involved in this process. Methods: A cell-based fluorometric assay was used to measure intracellular Ca (2+) concentrations ([Ca (2+)](i)) in RPE cells loaded with fura red-AM. Intracellular RPE ROS levels were measured by using the 5-(and 6)-chloromethyl-2',7'-dichlorodihydrofluorescence diacetate acetyl ester (CM-H(2)DCFDA) assay. RPE apoptosis was evaluated by activated caspase-3, Hoechst staining, and apoptosis ELISA. Results: MCP-1-activated human monocytes increased [Ca (2+)](i), ROS levels, and apoptosis in RPE cells, all of which were inhibited by 8-bromo-cyclic adenosine diphosphoribosyl ribose (8-Br-cADPR), an antagonist of cADPR. Although ROS scavengers, pyrrolidinedithiocarbamate (PDTC) and N -acetyl-cysteine (NAC), significantly inhibited ROS production and apoptosis induced by activated monocytes, they did not affect induced Ca(2+) levels. The induced Ca(2+) levels and apoptosis in RPE cells were inhibited by an antibody against cluster of differentiation antigen14 (CD14), an adhesion molecule expressed by these cells. Conclusions: Our results indicate that CD14, Ca(2+), and ROS are involved in activated monocyte-induced RPE apoptosis and that cADPR contributes to these changes. Understanding the complex interactions among CD14, cADPR, Ca(2+), and ROS may provide new insights and treatments of retinal diseases, including AMD.

PMID: 21447688 [PubMed - as supplied by publisher]

Genetics

PLoS One. 2011 Mar 24;6(3):e17784.

Using genetic variation and environmental risk factor data to identify individuals at high risk for age -related macular degeneration.

Spencer KL, Olson LM, Schnetz-Boutaud N, Gallins P, Agarwal A, Iannaccone A, Kritchevsky SB, Garcia M, Nalls MA, Newman AB, Scott WK, Pericak-Vance MA, Haines JL.

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Abstract

A major goal of personalized medicine is to pre-symptomatically identify individuals at high risk for disease using knowledge of each individual's particular genetic profile and constellation of environmental risk factors. With the identification of several well-replicated risk factors for age-related macular degeneration (AMD), the leading cause of legal blindness in older adults, this previously unreachable goal is beginning to seem less elusive. However, recently developed algorithms have either been much less accurate than expected, given the strong effects of the identified risk factors, or have not been applied to independent datasets, leaving unknown how well they would perform in the population at large. We sought to increase accuracy by using novel modeling strategies, including multifactor dimensionality reduction (MDR) and grammatical evolution of neural networks (GENN), in addition to the traditional logistic regression approach. Furthermore, we rigorously designed and tested our models in three distinct datasets: a Vanderbilt-Miami (VM) clinic-based case-control dataset, a VM family dataset, and the population-based Age-related Maculopathy Ancillary (ARMA) Study cohort. Using a consensus approach to combine the results from logistic regression and GENN models, our algorithm was successful in differentiating between high- and low-risk groups (sensitivity 77.0%, specificity 74.1%). In the ARMA cohort, the positive and negative predictive values were 63.3% and 70.7%, respectively. We expect that future efforts to refine this algorithm by increasing the sample size available for model building, including novel susceptibility factors as they are discovered, and by calibrating the model for diverse populations will improve accuracy.

PMID: 21455292 [PubMed - in process]

Hum Gene Ther. 2011 Mar 28. [Epub ahead of print]

Gene Transfer for Neovascular Age-Related Macular Degeneration.

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Abstract

Age-related macular degeneration (AMD) is a complex disease that has two phases, a degenerative phase often referred to as non-neovascular AMD (non- NVAMD) or dry AMD and a phase dominated by growth of new blood vessels in the subretinal space, NVAMD or wet AMD. Recent advances in the understanding of the molecular pathogenesis of NVAMD have led to new drug therapies that have provided major benefits to patients. However, those treatments require frequent intraocular injections that in many patients must be continued indefinitely to maintain visual benefits. Gene transfer to augment expression of endogenous antiangiogenic proteins is an alternative approach that has the potential to provide long term stability in patients with NVAMD. Studies in animal models that mimic aspects of NVAMD have identified several possible transgenes and a clinical trial in patients with advanced NVAMD has suggested that the approach may be feasible. Many important questions remain, but the rationale and preliminary data are compelling. The results of two ongoing clinical trials may answer several of the questions and help direct future research.

PMID: 21443427 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2011 Mar 29. [Epub ahead of print]

Association of Variants in LIPC and ABCA1 Genes with Intermediate and Large Drusen and Advanced Age-Related Macular Degeneration.

Yu Y, Reynolds R, Fagerness J, Rosner B, Daly MJ, Seddon JM.

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Purpose: The sub-phenotypes of intermediate and large drusen usually precede advanced age-related macular degeneration (AMD). There is little information about which genes influence drusen accumulation. Discovery of genetic variants associated with drusen may lead to prevention and treatments of AMD in its early stages.

Methods: A total of 3066 subjects were evaluated based on ocular examinations and fundus photography and categorized as controls (221), intermediate drusen (814), large drusen (949), or advanced AMD (1082). SNPs in the previously identified CFH, C2, C3, CFB, CFI, APOE, ARMS2/HTRA1 genes/regions, as well as the novel genes LIPC, CETP, ABCA1 in the high density lipoprotein (HDL) cholesterol pathway, were genotyped. Associations between stage of AMD and SNPs were assessed using logistic regression.

Results: Controlling for age, gender, education, smoking, body mass index, and antioxidant treatment, the number of minor (T) alleles of the genes LIPC and ABCA1 were significantly associated with a reduced risk of intermediate drusen (LIPC [p trend=0.045], ABCA1 [p=4.4x 10(-3)]), large drusen (LIPC [p=0.041], ABCA1 [p=7.7x 10(-4)]) and advanced AMD (LIPC [p=1.8x10(-3)], ABCA1 [p=3x10(-4)]). After further adjustment for known genetic factors, the protective effect of the TT genotype was significant for intermediate drusen (LIPC [Odds Ratio (OR) 0.56, 95% confidence interval (0.33-0.94)], ABCA1 [OR=0.48 (0.27-0.85)]), large drusen (LIPC [OR=0.58(0.34-0.98)], ABCA1 [OR=0.41(0.23-0.74)]) and advanced AMD (LIPC [OR=0.39(0.21-0.74)], ABCA1 [OR=0.35(0.17-0.71)]). CFH, C3, C2, and ARMS2/HTRA1 were associated with large drusen and advanced AMD.

Conclusions: LIPC and ABCA1 are related to intermediate and large drusen, as well as advanced AMD. CFH, C3, C2 and ARMS2/HTRA1 are associated with large drusen and advanced AMD.

PMID: 21447678 [PubMed - as supplied by publisher]

Ophthalmology. 2011 Mar 23. [Epub ahead of print]

Genetic Variants in Pigment Epithelium-Derived Factor Influence Response of Polypoidal Choroidal Vasculopathy to Photodynamic Therapy.

Nakata I, Yamashiro K, Yamada R, Gotoh N, Nakanishi H, Hayashi H, Tsujikawa A, Otani A, Ooto S, Tamura H, Saito M, Saito K, Iida T, Oishi A, Kurimoto Y, Matsuda F, Yoshimura N.

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PURPOSE: To investigate whether photodynamic therapy (PDT) outcomes of polypoidal choroidal vasculopathy (PCV) are related to baseline clinical characteristics, smoking history, or genetic factors by analyzing the retreatment-free period after the first PDT.

DESIGN: Retrospective cohort study.

PARTICIPANTS: The study consisted of 167 patients with PCV who underwent PDT as their first treatment.

METHODS: We targeted 638 single nucleotide polymorphisms (SNPs) in 42 possible susceptible genes for age-related macular degeneration to evaluate their relation to the effectiveness of PDT for PCV. For this evaluation, we used 2 methods: (1) survival analysis, with the retreatment-free period as the target; and (2) logistic regression test between the need for additional therapy within 3 months after the first PDT and the genotypes, with age, gender, smoking status, and greatest linear dimension (GLD) at baseline as covariates. The contributions of smoking status and GLD at baseline for the retreatment-free period also were evaluated. Contributions of these factors to visual prognosis were evaluated for 1 year after PDT.

MAIN OUTCOME MEASURES: Retreatment-free period after the first PDT for PCV. Secondary outcome

measures included correlation of the susceptible factor to the retreatment requirement within the 3-month follow-up and the mean visual acuity change.

RESULTS: In survival analyses, SERPINF1 rs12603825 showed a significant association with the retreatment-free period after the first PDT; those patients homozygous for the minor allele A of rs12603825 received additional treatment after PDT within significantly shorter times than those with other genotypes (P = 0.0038). There was no significant difference in the retreatment-free period between baseline GLD and smoking status. Retreatment within 3 months was required significantly more in patients with the AA genotype, even after taking into consideration the effect of clinical characteristics (age, gender), baseline PCV lesion size, and smoking status (P = 0.0027). Furthermore, patients with the AA genotype showed significantly worse visual prognosis after PDT (P = 0.013).

CONCLUSIONS: Pigment epithelium-derived factor (SERPINF1 or PEDF) polymorphisms may influence the initial response to and visual prognosis after PDT for PCV. Our findings may lead to understanding the pathogenesis of PCV and modification of the effects of PDT.

PMID: 21439646 [PubMed - as supplied by publisher]

Hum Mol Genet. 2011 Mar 29. [Epub ahead of print]

Copy number variations on chromosome 12q14 in patients with normal tension glaucoma.

Fingert JH, Robin AL, Stone JL, Roos B, Davis LK, Scheetz TA, Bennett SR, Wassink TH, Kwon YH, Alward WL, Mullins RF, Sheffield VC, Stone EM.

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Abstract

We report identification of a novel genetic locus (GLC1P) for normal tension glaucoma (NTG) on chromosome 12q14 using linkage studies of an African American pedigree (max NPL score = 19.7, max LOD score = 2.7). Subsequent comparative genomic hybridization and qPCR experiments identified a 780 kbp duplication within the GLC1P locus that is co-inherited with NTG in the pedigree. RT-PCR studies showed that the genes within this duplication (TBK1, XPOT, RASSF3, and GNS) are all expressed in human retina. Cohorts of 478 glaucoma patients (including 152 NTG patients), 100 normal control subjects, and 400 age-related macular degeneration patients were subsequently tested for copy number variation in GLC1P. Overlapping duplications were detected in two (1.3%) of the 152 NTG subjects, one of which had a strong family history of glaucoma. These duplications defined a 300 kbp critical region of GLC1P that spans two genes (TBK1 and XPOT). Microarray expression experiments and Northern blot analysis using RNA obtained from human skin fibroblast cells showed that duplication of chromosome 12q14 results in increased TBK1 and GNS transcription. Finally, immunohistochemistry studies showed that TBK1 is expressed in the ganglion cells, nerve fiber layer, and microvasculature of the human retina. Together, these data link the duplication of genes on chromosome 12q14 with familial NTG and suggest that an extra copy of the encompassed TBK1 gene is likely responsible for these cases of glaucoma. However, animal studies will be necessary to rule out a role for the other duplicated or neighboring genes.

PMID: 21447600 [PubMed - as supplied by publisher]

Pre-clinical

J Biomed Mater Res A. 2011 Mar 25. doi: 10.1002/jbm.a.33050. [Epub ahead of print]

Elastin-like recombinamers as substrates for retinal pigment epithelial cell growth.

Srivastava GK, Martín L, Singh AK, Fernandez-Bueno I, Gayoso MJ, Garcia-Gutierrez MT, Girotti A, Alonso M, Rodríguez-Cabello JC, Pastor JC.

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Abstract

The aim of this study is to investigate the use of elastin-like recombinamers (ELRs) as a substrate that can maintain the growth, phenotype, and functional characteristics of retinal pigment epithelial (RPE) cells efficiently and as a suitable carrier for the transplantation of autologous RPE cells for treatment of age-related macular degeneration (AMD). ELR films containing a bioactive sequence, RGD (ELR-RGD), and one with no specific sequence (ELR-IK) as control, were obtained by solvent-casting onto glass and subsequent cross-linking. ARPE19 cells were seeded on sterilized ELR films as well as on the control surfaces. Cells were analysed after 4, 24, 72, and 120 h to study cell adhesion, proliferation, cell viability, morphology, and specificity by staining with Trypan blue, DAPI, Rhodamin-Phalloidin and RPE65, ZO-1 antibodies and observing under fluorescence as well as electron microscope. ARPE19 cells seeded on both ELR films and controls were 100% viable and maintained their morphology and set of characteristics at the different time points studied. Cell proliferation on ELR-RGD was significantly higher than that found on ELR-IK at all time points, although it was less than the growth rate on polystyrene. ARPE19 cells grow well on ELR-RGD maintaining their phenotype. These results should be extended to further studies with fresh human RPE cells and in vivo studies to determine whether this ELR-RGD matrix could be used as a Bruch's membrane prosthesis and carrier for transplantation of RPE cells in patients suffering with AMD. © 2011 Wiley Periodicals, Inc. J Biomed Mater Res Part A:, 2011.

PMID: 21442725 [PubMed - as supplied by publisher]

J Biol Chem. 2011 Mar 23. [Epub ahead of print]

Polyethylene glycol (PEG) induced mouse model of choroidal neovascularization.

Lyzogubov VV, Tytarenko RG, Liu J, Bora NS, Bora PS.

Jones Eye Institute, Pat & Willard Walker Eye.

Abstract

In this study, we have described a new method of inducing choroidal neovascularization (CNV) in C57BL/6 mice, an animal model of wet type age-related macular degeneration (AMD). AMD is a disease that causes central blindness in humans. We injected polyethylene glycol-8 (PEG-8) subretinally in different doses (0.125-2 mg) to induce CNV. After the PEG-8 injection, we examined CNV at several time points (days 3-42). We also used Western blotting, immunohistochemistry and enzyme-linked immunosorbent assay (ELISA) to examine the complement component C3 split products, C9, vascular endothelial growth factor (VEGF), transforming growth factor beta 2 (TGF-beta2) and fibroblast growth factor basic (FGFb). As early as day 1, after treatment, we found that a single subretinal injection of 1 mg PEG-8 increased the C3 split products and the C9, TGF-beta2 and FGFb levels in the retinal pigment epithelium-choroid tissue. By day 3, after the PEG-8 injection, the intraocular activation of the complement system caused induction and progression of CNV including new vessels penetrating the Bruchs membrane. Then at day 5 after PEG-8 injection we observed a fully-developed CNV and retinal degeneration. Thus, in this study, we present a new, inexpensive, and an accelerated mouse model of CNV that may be useful to study AMD.

PMID: 21454496 [PubMed - as supplied by publisher]