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Drug treatment

Graefes Arch Clin Exp Ophthalmol. 2011 Aug 19. [Epub ahead of print]

Intravitreous VEGF-A in eyes with massive vitreous hemorrhage.

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PURPOSE/BACKGROUND: Although vascular endothelial growth factor (VEGF) is abundant in serum, the intraocular concentration of VEGF in eyes with massive vitreous hemorrhage (VH) is not well-known. The present study was conducted to elucidate the effects of a massive VH on intravitreous VEGF concentration.

METHODS: Vitreous samples were obtained during vitrectomy: 12 samples from eyes with epiretinal membrane without diabetic retinopathy (DR), and nine samples from massive VH with no DR, such as age-related macular degeneration, rhegmatogenous VH, Terson's syndrome and macro-aneurysm rupture. Twelve samples were obtained from proliferative DR. VEGF was measured with an enzyme-linked immunosorbent assay (ELISA). Samples incubated with or without heparin were also examined for the release of VEGF binding to the vitreous body. The localization of VEGF and type II collagen in the vitreous was evaluated from immunohistochemistry.

RESULTS: The concentration of VEGF was significantly higher in eyes with proliferative DR (821 ± 949 pg/ml) than in non-DR with massive VH (2.75 ± 7.5 pg/ml, $P < 0.01$, chi-square test) or non-DR with no VH (less than detectable level, $P < 0.01$, chi-square test) There was no statistically significant difference between eyes with massive VH and non-diabetic eyes without VH. Treatment with heparin did not significantly affect the concentration of vitreous VEGF. VEGF was localized mainly in the clot from the results of an immunohistochemical analysis.

CONCLUSIONS: Even with a massive VH, diffusible VEGF does not increase significantly in the liquid phase and is principally present in a clot. VH alone should not be an indication for vitrectomy from the point of view of VEGF-related pathology.

PMID: 21853228 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2011;5:1079-82. Epub 2011 Apr 8.

Single intravitreal ranibizumab for myopic choroidal neovascularization.

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Abstract

We report a case of myopic choroidal neovascularization that showed improvement after a single injection of ranibizumab. A 45-year-old Chinese man with high myopia presented with sudden onset painless central scotoma of his right eye of 2 weeks' duration. There was no history of trauma. His right eye vision on presentation was 6/30 which showed no improvement with pinhole. The right fundus showed myopic maculopathy at the posterior pole with subretinal hemorrhage at the inferotemporal fovea. The optic disc was tilted with inferotemporal peripapillary atrophy. There was a myopic maculopathy appearance in the macula of the left eye. Fundus fluorescein angiography revealed choroidal neovascularization at the fovea of the right eye. A diagnosis of right eye choroidal neovascularization secondary to myopic maculopathy was made. A single intravitreal injection of ranibizumab 0.05 mL was given. Ten weeks following intravitreal injection, vision had improved to 6/7.5, and repeated fundus fluorescein angiography showed absence of choroidal neovascularization. Follow-up at 6 months showed visual acuity had normalized to 6/6 with glasses, which was maintained up to 12 months following treatment. The right fundus showed no further subretinal hemorrhage with no new lesions.

PMID: 21847340 [PubMed - in process]

Pharmacol Res. 2011 Jun 21. [Epub ahead of print]

The non-antibiotic properties of tetracyclines: Clinical potential in ophthalmic disease.

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INTRODUCTION: Beyond their decades of long use as broad-spectrum antibiotics, tetracyclines and their derivatives have been shown to exhibit non-antimicrobial properties including their ability to interact with matrix metalloproteinases (MMP), tissue inhibitors of MMPs, growth factors and cytokines. As such, they are capable of affecting inflammation, immunomodulation, cell proliferation, and angiogenesis. Although they have been used to treat a variety of conditions including acne, cutaneous sarcoid, and rheumatoid arthritis, amongst others, their use in treating ophthalmologic disease is in its infancy.

MATERIALS AND METHODS: A literature review on the role of non-antimicrobial properties of tetracyclines, semisynthetic tetracyclines, and chemically modified non-antibacterial tetracyclines (CMTs) and their clinical properties was performed. The effects of these compounds in relation to ophthalmic disease are presented.

RESULTS: Due to their non-antimicrobial properties, tetracyclines and their derivatives are capable of influencing a wide variety of ocular diseases in animal models. By affecting expression of MMP-9 and tumor necrosis factor (TNF)-α, these compounds decrease corneal permeability, improve corneal smoothness, and reduce meibomian gland dysfunction; this improves the tear film which in turn restores the optical quality of the tear film and cornea. Sterile corneal ulceration may be inhibited via anticollagenase activity; this has been demonstrated in both animal models and case reports. CMTs suppress cataractogenesis in a diabetic rat model, possibly by affecting MMPs. With respect to retinal disease, tetracyclines can inhibit both microglial-mediated cell death and retinal cell apoptosis as well as prevent retinal capillary damage via caspase inhibition thus preventing retinal neovascularization. Experimental choroidal neovascularization is reduced by inhibition of MMP-2 and MMP-9, elevation of pigment epithelial derived growth factor (PEDF), and reduction of vascular endothelial growth factor (VEGF) expression via Fas ligand.

DISCUSSION: Due to their non-antimicrobial properties, tetracyclines and their derivatives are capable of

influencing a wide variety of ocular disease in animal models. Research suggests that they are able to reduce inflammation in the eyelid meibomian glands, improve optical clarity of the cornea, retard cataract formation, and limit ocular angiogenesis. They may have a role in treating the leading causes of vision loss: cataract, age-related macular degeneration, and diabetic retinopathy, all of which are anticipated to increase in incidence due to the aging population.

CONCLUSIONS: Tetracyclines, semisynthetic tetracyclines, and CMTs may have a role in the treatment of several important ophthalmologic diseases; however, further research is required, including prospective multicenter clinical trials.

PMID: 21843641 [PubMed - as supplied by publisher]

Curr Med Chem. 2011 Aug 15. [Epub ahead of print]

Nucleic Acid Aptamers: Clinical Applications and Promising New Horizons.

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Aptamers are a special class of nucleic acid molecules that are beginning to be investigated for clinical use. These small RNA/DNA molecules can form secondary and tertiary structures capable of specifically binding proteins or other cellular targets; they are essentially a chemical equivalent of antibodies. Aptamers have the advantage of being highly specific, relatively small in size, and non-immunogenic. Since the discovery of aptamers in the early 1990s, great efforts have been made to make them clinically relevant for diseases like cancer, HIV, and macular degeneration. In the last two decades, many aptamers have been clinically developed as inhibitors for targets such as vascular endothelial growth factor (VEGF) and thrombin. The first aptamer based therapeutic was FDA approved in 2004 for the treatment of age-related macular degeneration and several other aptamers are currently being evaluated in clinical trials. With advances in targeted -therapy, imaging, and nanotechnology, aptamers are readily considered as potential targeting ligands because of their chemical synthesis and ease of modification for conjugation. Preclinical studies using aptamer-siRNA chimeras and aptamer targeted nanoparticle therapeutics have been very successful in mouse models of cancer and HIV. In summary aptamers are in several stages of development, from preclinical studies to clinical trials and even as FDA approved therapeutics. In this review, we will discuss the current state of aptamers in clinical trials as well as some promising aptamers in pre-clinical development.

PMID: 21838685 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Am J Ophthalmol. 2011 Aug 17. [Epub ahead of print]

Retinal and Choroidal Thickness in Early Age-Related Macular Degeneration.

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PURPOSE: To compare retinal thickness and choroidal thickness at increasing retinal eccentricity in individuals with early age-related macular degeneration (AMD) and in healthy controls using enhanced choroidal penetration, 3-dimensional optical coherence tomography at 1060 nm.

DESIGN: Cross-sectional study.

METHODS: Individuals with early AMD (n = 16; mean age, 71.6 ± 8.5 years) and a comparison group of healthy controls (n = 16; 67.6 ± 5.4 years) were recruited. Three-dimensional (20 degrees × 20 degrees) long-wavelength optical coherence tomography (1060 nm) images (approximately 8-μm axial resolution; 47 000 A scans/second, centered on the fovea) were obtained from all participants after pupil dilation. Retinal thickness was measured between the inner limiting membrane and the retinal pigment epithelium. Choroidal thickness was measured between the retinal pigment epithelium and the choroid-scleral interface. Thickness measurements were obtained subfoveally and at 0.5-mm intervals to a maximum of 2.0 mm nasally, temporally, superiorly, and inferiorly. The main outcome measures were retinal and choroidal thickness (measured in micrometers) at different eccentricities on vertical and horizontal meridians.

RESULTS: Mean retinal thickness was reduced significantly in the group of participants with early AMD compared with the control group at multiple locations within 2.0 mm of the fovea. This difference was most significant at the fovea, where the mean retinal thickness of the early AMD group was 179 ± 27 μm and that of the control group was 202 ± 18 μm (P = .008). There was no significant difference in choroidal thickness between groups at any location.

CONCLUSIONS: Retinal thickness is reduced in early AMD, but choroidal thickness seems to be unaffected by the early disease process.

PMID: 21851922 [PubMed - as supplied by publisher]

Epidemiology

Am J Ophthalmol. 2011 Aug 13. [Epub ahead of print]

Medicare Costs for Neovascular Age-Related Macular Degeneration, 1994-2007.

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PURPOSE: To assess changes in Medicare payments for neovascular age-related macular degeneration (AMD) since introduction of anti-vascular endothelial growth factor (VEGF) therapies.

DESIGN: Retrospective, longitudinal cohort study.

METHODS: Using the Medicare 5% sample, beneficiaries with new diagnoses of neovascular AMD in 1994 (N = 2497), 2000 (N = 3927), and 2006 (N = 6041) were identified using International Classification of Diseases (ICD-9-CM). The total first-year health care and eye care costs were calculated for each beneficiary. Propensity score matching was used to match individuals in the 2000 and 2006 cohorts with the 1994 cohort on age, sex, race, Charlson Comorbidity Index, and low vision/blindness.

RESULTS: The number of beneficiaries newly diagnosed with neovascular AMD more than doubled between the 1994 and 2006 cohorts. Overall yearly Part B payments per beneficiary increased significantly from $3567 for the 1994 to $5991 for the 2006 cohort (P < .01) in constant 2008 dollars. Payments for eye care alone doubled from $1504 for the 1994 cohort to $3263 for the 2006 cohort (P < .01). Most of the increase in payments for eye care in 2006 reflected payments for anti-VEGF injections, which were $1609 over 1 year. Mean annual numbers of visits and imaging studies also increased significantly between the 1994 and 2006 cohort. Results were similar in the matched sample.

CONCLUSIONS: The introduction of anti-VEGF intravitreal injections has offered remarkable clinical benefits for patients with neovascular AMD, but these benefits have come at the cost of an increased financial burden of providing care for these patients.

PMID: 21843875 [PubMed - as supplied by publisher]

Pathogenesis

Mol Vis. 2011;17:2040-8. Epub 2011 Jul 27.

Protective effect of canolol from oxidative stress-induced cell damage in ARPE-19 cells via an ERK mediated antioxidative pathway.

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PURPOSE: Oxidative stress damage to retinal pigment epithelial (RPE) cells is thought to play a critical role in the pathogenesis of age-related macular degeneration (AMD). This study was conducted to investigate the protective effect of canolol against oxidative stress-induced cell death in ARPE-19 cells and its underlying mechanism.

METHODS: ARPE-19 cells, a human retinal pigment epithelial cell line, were subjected to oxidative stress with 150 μM t-butyl hydroxide (t-BH) in the presence/absence of canolol in different concentrations. Cell viabilities were monitored by a 3-(4, 5-dimethylthiazol-2-yl)-2, 5 diphenyl tetrazolium bromide (MTT) assay. The apoptosis was measured by flow cytometry using Annexin V-FITC and PI staining and intracellular reactive oxygen species (ROS) levels were measured by a fluorescence spectrophotometer. Gene expression of NF-E2-related factor (Nrf-2), heme oxygenase-1 (HO-1), catalase and glutathione S-transferase-pi (GST-pi) were measured by a reverse transcription polymerase chain reaction (RT-PCR) assay. Activation of the extracellular signal regulated kinase (ERK) protein was evaluated by western blot analysis.

RESULTS: Canolol showed relatively high safety for ARPE-19 cells and recovered the cell death caused by t-BH dose-dependently at a concentration of 50-200 μM. Canolol also reduced t-BH-induced intracellular ROS generation and thus protected ARPE-19 cells from cell apoptosis. HO-1, catalase, GST-pi, and Nrf-2 were elevated in ARPE-19 cells after treatment with different concentrations of canolol for 24 h. Finally, canolol was found to activate extracellular signal regulated kinase (ERK) phosphorylation in ARPE-19 cells under the condition, with or without t-BH.

CONCLUSIONS: Canolol protected ARPE-19 cells from t-BH-induced oxidative damage and the protective mechanism was associated, at least partly, with the upregulation (activation) of antioxidative enzymes, probably through an ERK mediated pathway. This suggests that canolol offers a remarkable protective effect against oxidative damage of RPE cells and may have a therapeutic effect on AMD and other oxidative stress-related retinal diseases.

PMID: 21850179 [PubMed - in process]

Curr Eye Res. 2011 Sep;36(9):838-49.

Hypoxia Specific SDF-1 Expression by Retinal Pigment Epithelium Initiates Bone Marrow-derived Cells to Participate in Choroidal Neovascularization in a Laser-induced Mouse Model.

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Purpose: Choroidal neovascularization (CNV) is a major cause of vision loss in patients with age-related macular degeneration (AMD). Stromal cell-derived factor-1 (SDF-1)/CXC chemokine receptor 4 (CXCR4) plays a critical role in homing of bone marrow-derived cells (BMCs) to choroidal neovascularization (CNV). In this study, we investigated the contribution of hypoxia specific HIF-1α-induced SDF-1 expression in retinal pigment epithelium (RPE) cells and the potential role of SDF-1 in CNV formation.

Materials and Methods: Green fluorescent protein (GFP) chimeric mice were developed by transplanting bone marrow cells of gfp(+/+) transgenic mice to sublethally irradiated C57BL/6J mice. CNV was induced by laser photocoagulation. Ocular tissue was processed for immunofluorescence to detect HIF-1α and SDF -1 expression, and cell surface markers such as CXCR4, CD34 and CD31 and so on during CNV formation. In vitro, adult human RPE (hRPE) cells were cultured under conditions of chemical hypoxia using CoCl(2) administration. And RNAi technique was used to knock down HIF-1α gene to observe the expression of HIF -1α and SDF-1 in hRPE cells.

Results: BMCs trafficked around laser lesion adjacent to RPE layer 4 h after laser photocoagulation, where SDF-1 expression was relatively higher. With increasing expression of SDF-1, more BMCs were infiltrated into laser lesion to participate in CNV, and both reached peak at 3 d ($p < 0.05$). About 81% BMCs involved in CNV were CXCR4(+). Many of them acquired the surface marker of endothelial precursor cells (CD34 (+)) and endothelial cells (CD31(+)). The constituent ratio of CD34(+) and CD31(+) BMCs increased with SDF-1 expression. In vitro, we proved that hypoxia specific-HIF-1α influenced SDF-1 expression in hRPE cells.

Conclusions: These findings suggested that hypoxia-induced SDF-1 expression in RPE might be a critical initiator for recruitment of BMCs in CNV. SDF-1 might be another important factor in BMCs' differentiation into endothelial cells to participate in the CNV.

PMID: 21851170 [PubMed - in process]

Mol Vis. 2011;17:1901-8. Epub 2011 Jul 14.

A robust model for simultaneously inducing corneal neovascularization and retinal gliosis in the mouse eye.

Paranthan RR, Bargagna-Mohan P, Lau DL, Mohan R.

PURPOSE:To develop an animal model for simultaneously eliciting corneal angiogenesis and retinal gliosis that will enable the assessment of inhibitor efficacy on these two pathological processes in separate anatomic sites of the ocular globe.

METHODS: Four to six week-old mice in a C57BL/6J background were anesthetized and 0.15 N NaOH was applied to the cornea, followed by mechanical scraping of the epithelium from limbus and central cornea. After this injury, mice were treated with vehicle or with an inhibitor (withaferin A [WFA]), which were delivered by intraperitoneal injection, to assess the pharmacological effects on angiogenesis and/or gliosis. Mice were sacrificed after 14 days and tissues (corneas and retinas) were prepared for analysis of corneal neovascularization and retinal gliosis by immunohistochemistry and western blotting, respectively. This protocol was also suited for studying earlier disease end points, for assessment of drug dose efficacy or genetic influences and the entire procedure and this analysis was completed in 16-17 days.

RESULTS: Both corneal angiogenesis and retinal gliosis were maximally sustained at fourteen days following chemical and mechanical injury of the cornea. 1) Injured corneas showed abundant CD31(+) staining, with new blood vessels branching out from the limbus to the central cornea. WFA treatment potently inhibited corneal neovascularization. 2) Retinal gliosis in injured mice was associated with upregulated expression of glial fibrillary acidic protein (GFAP) that appeared as polymeric filaments and soluble forms expressed in reactive Müller glial cells. WFA treatment potently downregulated the expression of soluble and filamentous GFAP; the latter protein was fragmented.

CONCLUSIONS: We have developed a mouse model for investigating retinal gliosis and corneal neovascularization. We used this model to demonstrate the simultaneous inhibitory effects of WFA on both of these disease processes. Retinal gliosis occurs in several major degenerative conditions of the eye, including age -related macular degeneration, where angiogenesis is also a prevailing pathological feature. Thus, inhibitors of both gliosis and angiogensis used as combination therapy are currently being explored for treatment

of such complex diseases. The model presented here affords a very simple preclinical assay for screening combination of drugs or polypharmacological agents and reduces the numbers of animals because of the different anatomic sites of these pathologies. Finally, given that endogenous mediators elicit angiogenesis and gliosis in this model, the combination of genetics and pharmacology can be exploited to study drug mechanisms and for target validation in vivo.

PMID: 21850164 [PubMed - in process]

Mol Vis. 2011;17:1839-49. Epub 2011 Jul 8.

Photo-products of retinal pigment epithelial bisretinoids react with cellular thiols.

Yoon KD, Yamamoto K, Zhou J, Sparrow JR.

PURPOSE: Bisretinoids such as A2E that accumulate as components of the lipofuscin of retinal pigment epithelial cells are implicated in some retinal disease processes. These compounds undergo light-induced oxidation and cleavage with the latter releasing of a mixture of aldehyde-bearing fragments, including dicarbonyl methylglyoxal. We tested for the reactivity of photooxidation and photodegradation products of A2E with thiol-containing glutathione (GSH).

METHODS: In cell-free assays, we measured the ability of photooxo-A2E to competitively inhibit the GSH-mediated reduction of the thiol reagent 5,5'-dithiobis-(2-nitrobenzoic acid). Cellular GSH was assayed colorimetrically. Products of GSH reduction and GSH-adducts were detected by electrospray ionization mass spectrometry (ESI-MS) and GSH and oxidized GSH (glutathione disulfide [GSSG]) were quantified from chromatographic peak areas.

RESULTS: We found that GSH can donate hydrogen atoms to, and form conjugates with, photooxidized forms of the bisretinoid A2E and with its photocleavage products. Reaction with non-photooxidized A2E was not observed. Chemical reduction by GSH involved the donation of a hydrogen atom from each of two GSHs. The ratio of GSH consumed to GSSG formed was consistent with GSH being used for both reduction and adduct formation. With the aid of synthesized standards, methylglyoxal-GSH adducts were identified within mixtures of GSH and photooxidized A2E; the adducts formed noncatalytically and by glutathione-S-transferase mediation.

CONCLUSIONS: Reduction and adduct formation by GSH likely limits the reactivity of bisretinoid photoproducts and may aid their elimination from the cells. These findings are significant to forms of macular degeneration associated with bisretinoid formation and maculopathy stemming from GSH synthase deficiency.

PMID: 21850158 [PubMed - in process]

Proc Natl Acad Sci U S A. 2011 Aug 15. [Epub ahead of print]

Increased expression of multifunctional serine protease, HTRA1, in retinal pigment epithelium induces polypoidal choroidal vasculopathy in mice.

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Abstract

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the elderly. Wet AMD includes typical choroidal neovascularization (CNV) and polypoidal choroidal vasculopathy (PCV).

The etiology and pathogenesis of CNV and PCV are not well understood. Genome-wide association studies have linked a multifunctional serine protease, HTRA1, to AMD. However, the precise role of HTRA1 in AMD remains elusive. By transgenically expressing human HTRA1 in mouse retinal pigment epithelium, we showed that increased HTRA1 induced cardinal features of PCV, including branching networks of choroidal vessels, polypoidal lesions, severe degeneration of the elastic laminae, and tunica media of choroidal vessels. In addition, HTRA1 mice displayed retinal pigment epithelium atrophy and photoreceptor degeneration. Senescent HTRA1 mice developed occult CNV, which likely resulted from the degradation of the elastic lamina of Bruch's membrane and up-regulation of VEGF. Our results indicate that increased HTRA1 is sufficient to cause PCV and is a significant risk factor for CNV.

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Graefes Arch Clin Exp Ophthalmol. 2011 Aug 17. [Epub ahead of print]

Neural stem/progenitor cells circulating in peripheral blood of patients with neovascular form of AMD: a novel view on pathophysiology.

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BACKGROUND: The neovascular form of age-related macular degeneration (AMD) manifested with choroidal neovascularization (CNV) is one of the leading causes of rapid and irreversible visual loss. Recent reports suggest that bone marrow-derived stem/progenitor cells (SPCs) play a crucial role in the development and progression of the disease. The purpose of this study was to investigate whether or not undifferentiated non-haematopoietic stem cells, including those capable of differentiating into neural phenotypes, play a role in the pathological state of CNV formation.

METHODS: Peripheral blood samples were collected from 46 patients diagnosed with CNV and from 46 controls. The CXCR4(+)Lin(-)CD45(-) stem cells were counted and analysed by flow cytometry. Using qRT-PCR and immunocytofluorescence, the expression of early neural and glial cell markers (β-III-tubulin, nestin, and glial fibrillary acidic protein) in the sorted cells was analysed, and correlated with plasma concentrations of stromal cell-derived factor 1 (SDF-1) (enzyme-linked immunosorbent assay), which is a pivotal chemokine that regulates the trafficking of SPCs.

RESULTS: We found that the number of circulating CXCR4(+)Lin(-)CD45(-) cells did not differ in patients with active CNV as compared to the controls. However, we noticed significant intracellular overexpression of β-III-tubulin in the cells derived from AMD patients. Moreover, we observed significantly lower SDF-1 plasma levels in neovascular AMD patients compared to healthy individuals.

CONCLUSIONS: Our findings suggest that neural progenitor cells, together with low SDF-1 concentrations, may play a considerable role in the process of AMD progression. Further investigations aimed at the precise elucidation of these issues may help with the future development of effective prevention against, and the treatment of, this disease.

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Genetics

Mol Vis. 2011;17:2080-92. Epub 2011 Aug 6.

Copy number variation in the complement factor H-related genes and age-related macular degeneration.

Kubista KE, Tosakulwong N, Wu Y, Ryu E, Roeder JL, Hecker LA, Baratz KH, Brown WL, Edwards AO.

PURPOSE: To determine the contribution of copy number variation (CNV) in the regulation of complement activation (RCA) locus to the development of age-related macular degeneration (AMD).

METHODS: A multiplex ligation-dependent probe amplification assay was developed to quantify the number of copies of CFH, CFHR3, CFHR1, CFHR4, CFHR2, and CFHR5 in humans. Subjects with (451) and without (362) AMD were genotyped using the assay, and the impact on AMD risk was evaluated.

RESULTS: Eight unique combinations of copy number variation were observed in the 813 subjects. Combined deletion of CFHR3 and CFHR1 was protective (OR=0.47, 95% confidence interval 0.36-0.62) against AMD and was observed in 88 (82 [18.6%] with one deletion, 6 [1.4%] with two deletions) subjects with AMD and 127 (108 [30.7%] with one deletion, 19 [5.4%] with two deletions) subjects without AMD. Other deletions were much less common: CFH intron 1 (n=2), CFH exon 18 (n=2), combined CFH exon 18 and CFHR3 (n=1), CFHR3 (n=2), CFHR1 (n=1), combined CFHR1 and CFHR4 (n=15), and CFHR2 deletion (n=7, 0.9%). The combined CFHR3 and CFHR1 deletion was observed on a common protective haplotype, while the others appeared to have arisen on multiple different haplotypes.

CONCLUSIONS: We found copy number variations of CFHR3, CFHR1, CFHR4, and CFHR2. Combined deletion of CFHR3 and CFHR1 was associated with a decreased risk of developing AMD. Other deletions were not sufficiently common to have a statistically detectable impact on the risk of AMD, and duplications were not observed.

PMID: 21850184 [PubMed - in process]

Immunobiology. 2011 Jul 23. [Epub ahead of print]

Variation in complement component C1 inhibitor in age-related macular degeneration.

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Abstract

This study assessed variation in plasma levels of the complement regulatorC1 inhibitor (C1inh) in patients with age related macular degeneration (AMD) and controls. Plasma from391 AMD cases and 370 controls was assayed by rate nephelometry to determine C1inh protein levels. Protein levels were analysed for relationships with age, gender, smoking, AMD disease status and genetic variation in the SERPING1 gene, which encodes C1inh, using a multivariate analysis. t-Tests show a significant difference in C1inh levels in AMD cases compared with controls (p=2.340E-6), smokers compared to non-smokers (p=1.022E-4) and females compared to males (p=1.661E-7). Multivariate analysis shows that after accounting for gender and smoking AMD status remained significant. Age was included in the model but was not significant. Including genetic variation in the model shows that one significant SNP (rs2649663) 5' of the SERPING1 gene is associated with C1inh levels though this SNP is not associated with AMD. This suggests that genetic variation in the promoter region of the SERPING1 gene may influence expression of the gene.

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Diet

BMC Ophthalmol. 2011 Aug 18;11(1):22. [Epub ahead of print]

Cholesterol-Enriched Diet Causes Age-Related Macular Degeneration-Like Pathology in Rabbit retina.

Dasari B, Prasanthi JR, Marwarha G, Singh BB, Ghribi O.

BACKGROUND: Alzheimer's disease (AD) and age-related macular degeneration (AMD) share several pathological hallmarks including beta-amyloid (Abeta) accumulation, oxidative stress, and apoptotic cell death. The causes of AD and AMD are likely multi-factorial with several factors such as diet, environment, and genetic susceptibility participating in the pathogenesis of these diseases. Epidemiological studies correlated high plasma cholesterol levels with high incidence of AD, and feeding rabbits with a diet rich in cholesterol has been shown to induce AD-like pathology in rabbit brain. High intake of cholesterol and saturated fat were also long been suspected to increase the risk for AMD. However, the extent to which cholesterol-enriched diet may also cause AMD-like features in rabbit retinas is not well known.

METHODS: Male New Zealand white rabbits were fed normal chow or a 2% cholesterol-enriched diet for 12 weeks. At necropsy, animals were perfused with Dulbecco's phosphate-buffered saline and the eyes were promptly removed. One eye of each animal was used for immunohistochemistry and retina dissected from the other eye was used for Western blot, ELISA assays, spectrophotometry and mass spectrometry analyses.

RESULTS: Increased levels of Abeta, decreased levels of the anti-apoptotic protein Bcl-2, increased levels of the pro-apoptotic Bax and gadd153 proteins, emergence of TUNEL-positive cells, and increased generation of reactive oxygen species were found in retinas from cholesterol-fed compared to normal chow-fed rabbits. Additionally, astrogliosis, drusen-like debris and cholesterol accumulation in retinas from cholesterol-fed rabbits were observed. As several lines of evidence suggest that oxidized cholesterol metabolites (oxysterols) may be the link by which cholesterol contributes to the pathogenesis of AMD, we determined levels of oxysterols and found a dramatic increase in levels of oxysterols in retinas from cholesterol-fed rabbits.

CONCLUSIONS: Our results suggest that cholesterol-enriched diets cause retinal degeneration that is relevant to AMD. Furthermore, our data suggests high cholesterol levels and subsequent increase in the cholesterol metabolites as potential culprits to AMD.

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Graefes Arch Clin Exp Ophthalmol. 2011 Aug 18. [Epub ahead of print]

Effect of 1-year lutein supplementation on macular pigment optical density and visual function.

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BACKGROUND: Although it is known that antioxidants including lutein can affect macular pigment optical density (MPOD) and visual function, we still have much to learn about their effect. Our aim was to assess the 1-year changes in MPOD and visual function in response to supplementation containing lutein.

METHODS: We prospectively measured the MPOD level of those who received a supplement containing 6 mg of lutein daily for 1 year. MPOD level was measured every 3 months by using autofluorescence spectrometry with the two-wavelength method. Other examinations, including contrast sensitivity and retinal sensitivity were also measured every 3 or 6 months. Stepwise regression analysis was performed to determine

the factors that correlated with the changes observed in those examinations.

RESULTS: Forty-three eyes of 43 Japanese subjects, including five normal eyes, five fellow eyes with central serous chorioretinopathy (CSC), and 33 fellow eyes with age-related macular degeneration (AMD) were enrolled. The higher baseline MPOD level was correlated with the eye with a clear intraocular lens (IOL). Although no time-dependent changes in the MPOD level were obtained in any area, subjects without cardiovascular diseases showed higher increase in the MPOD level. We observed significant increases in the contrast sensitivity at 1 year ($p = 0.0124$) and in the retinal sensitivity at 6 months ($p < 0.0001$) and 1 year ($p < 0.0001$). Stepwise regression analysis showed that nonsmokers had increased contrast sensitivity ($p = 0.0173$), and the fellow eye of those with CSC had less of an increase in retinal sensitivity ($p = 0.0491$).

CONCLUSIONS: Daily supplementation with 6 mg of lutein did not affect the MPOD level for 1 year, suggesting that 6 mg of lutein may be insufficient to increase the MPOD level. However, supplementation seems to improve visual functions such as contrast sensitivity and retinal sensitivity.

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