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# MD Research News

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## Drug treatment

**N Engl J Med. 2011 Apr 28. [Epub ahead of print]**

**Bevacizumab versus Ranibizumab - The Verdict.**

Rosenfeld PJ.

From the Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami.

Abstract

For 5 years, patients and clinicians have wrestled with the choice between two drugs for the treatment of neovascular age-related macular degeneration (AMD), a common cause of irreversible blindness among the elderly worldwide. Vision loss results from the abnormal growth and leakage of blood vessels in the macula, a specialized portion of the retina responsible for the best visual acuity. Without this macular vision, patients become legally blind. Vascular endothelial growth factor (VEGF), the cytokine primarily responsible for blood-vessel growth, is inhibited when anti-VEGF drugs are injected repeatedly into the eye, and blindness is prevented in most patients. The majority . . .

PMID: 21526924 [PubMed - as supplied by publisher]

**N Engl J Med. 2011 Apr 28. [Epub ahead of print]**

**Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration.**

[No authors listed]

Background: Clinical trials have established the efficacy of ranibizumab for the treatment of neovascular age-related macular degeneration (AMD). In addition, bevacizumab is used off-label to treat AMD, despite the absence of similar supporting data.

Methods: In a multicenter, single-blind, noninferiority trial, we randomly assigned 1208 patients with neovascular AMD to receive intravitreal injections of ranibizumab or bevacizumab on either a monthly schedule or as needed with monthly evaluation. The primary outcome was the mean change in visual acuity at 1 year, with a noninferiority limit of 5 letters on the eye chart.

Results: Bevacizumab administered monthly was equivalent to ranibizumab administered monthly, with 8.0 and 8.5 letters gained, respectively. Bevacizumab administered as needed was equivalent to ranibizumab as needed, with 5.9 and 6.8 letters gained, respectively. Ranibizumab as needed was equivalent to monthly

ranibizumab, although the comparison between bevacizumab as needed and monthly bevacizumab was inconclusive. The mean decrease in central retinal thickness was greater in the ranibizumab-monthly group (196 µm) than in the other groups (152 to 168 µm, P=0.03 by analysis of variance). Rates of death, myocardial infarction, and stroke were similar for patients receiving either bevacizumab or ranibizumab (P>0.20). The proportion of patients with serious systemic adverse events (primarily hospitalizations) was higher with bevacizumab than with ranibizumab (24.1% vs. 19.0%; risk ratio, 1.29; 95% confidence interval, 1.01 to 1.66), with excess events broadly distributed in disease categories not identified in previous studies as areas of concern.

Conclusions: At 1 year, bevacizumab and ranibizumab had equivalent effects on visual acuity when administered according to the same schedule. Ranibizumab given as needed with monthly evaluation had effects on vision that were equivalent to those of ranibizumab administered monthly. Differences in rates of serious adverse events require further study. (Funded by the National Eye Institute; ClinicalTrials.gov number, NCT00593450 .).

PMID: 21526923 [PubMed - as supplied by publisher]

**Eye (Lond). 2011 Apr 29. [Epub ahead of print]**

**A review of safety incidents in England and Wales for vascular endothelial growth factor inhibitor medications.**

Kelly SP, Barua A.

Royal Bolton Hospital NHS Foundation Trust, Lancashire, UK.

Purpose: To learn from patient safety incidents (PSIs) following recent introduction of vascular endothelial growth factor inhibitor medications (anti-VEGF) in ophthalmic care, as reported via a national incident reporting database.

Methods: Thematic retrospective review of anti-VEGF medications PSIs as reported via clinical incident reporting methods in NHS care in England and Wales from 2003 to 2010, ascertained from database mining at the National Patient Safety Agency (NPSA).

Results: In all, 166 relevant anti-VEGF incidents were reported. Reports have increased year on year from 2006. Incident severity as reported: 10 were reported as 'severe harm' and 23 as 'moderate harm'. The remainder were 'low' or 'no harm' events. The incident themes and/or causes found and by order of severity included: intra-ocular inflammation/endophthalmitis (n=16); treatment or follow-up delays (n=45); wrong medication (n=26); wrong eye/patient injection (n=17); missing records (n=12). Other problems included medication availability and refrigeration failures. We reflect on potential solutions for addressing the matters found. Systemic safety matters, stroke, subdural hemorrhage, and myocardial infarction (total n=3) followed anti-VEGF treatments.

Conclusion: Although infrequent, anti-VEGF medication PSIs or errors do occur and are thus a threat to quality. This review also provides supporting evidence to existing concerns and challenges surrounding age -related macular degeneration service pressures and provision. Lessons for improvement of care from a national incident reporting database for a frequently undertaken and recently introduced ophthalmic procedure were found. Suggestions are proposed for improving quality by reducing such problems based on analysis of such reports. Endophthalmitis reports following intra-vitreal injections suggest rigorous infection control measures are required.Eye advance online publication, 29 April 2011; doi:10.1038/ eye.2011.89.

PMID: 21527957 [PubMed - as supplied by publisher]

**Br J Ophthalmol. 2011 Apr 27. [Epub ahead of print]**

**The effect of intravitreal ranibizumab on intraoperative bleeding during pars plana vitrectomy for diabetic traction retinal detachment.**

Ribeiro JA, Messias A, de Almeida FP, Costa RA, Scott IU, de Figueiredo-Pontes LL, Jorge R.

School of Medicine of Ribeirão Preto, Ribeirão Preto, São Paulo, Brazil.

PMID: 21527416 [PubMed - as supplied by publisher]

**Clin Exp Optom. 2011 Apr 25. doi: 10.1111/j.1444-0938.2011.00614.x. [Epub ahead of print]**

**Macular hole after intravitreal ranibizumab injection for polypoidal choroidal vasculopathy.**

Cho JH, Park SE, Han JR, Kim HK, Nam WH.

Department of Ophthalmology, Kangnam Sacred Heart Hospital, College of Medicine, Hallym University, Seoul, Korea Department of Ophthalmology, Hangang Sacred Heart Hospital, College of Medicine, Hallym University, Seoul, Korea, E-mail: eyedrnam@naver.com.

Abstract

A 67-year-old man visited the clinic presenting with the complaint of decreased vision in his left eye. Visual acuity of the left eye was 6/6. On fundus examination, an orange polypoidal lesion and retinal pigment epithelial (RPE) detachment were seen. Fluorescein angiography and indocyanine green angiography were performed. There was hyperfluorescence of a clustered polyp-like lesion. The patient was diagnosed with polypoidal choroidal vasculopathy and we recommended that he be seen again in three months. At this visit, visual acuity of the left eye had decreased to 6/9 and the RPE detachment was aggravated. Intravitreal injection of ranibizumab was performed. One month after the injection, visual acuity of his left eye was 6/96. A macular hole was seen in his left eye and vitrectomy of the left eye was performed. Optical coherence tomography was checked and it showed that the macular hole was closed. Two more intravitreal ranibizumab injections were done on the left eye. Visual acuity of his left eye subsequently improved to 6/18.8.

PMID: 21517972 [PubMed - as supplied by publisher]

## Other treatment & diagnosis

**J Cell Physiol. 2011 Apr 25. doi: 10.1002/jcp.22814. [Epub ahead of print]**

**Pluripotent human stem cells for the treatment of retinal disease.**

Rowland TJ, Buchholz DE, Clegg DO.

SourceCenter for Stem Cell Biology and Engineering; Department of Molecular, Cellular and Developmental Biology; Neuroscience Research Institute.

Abstract

Despite advancements made in our understanding of ocular biology, therapeutic options for many debilitating retinal diseases remain limited. Stem cell-based therapies are a potential avenue for treatment of retinal disease, and this minireview will focus on current research in this area. Cellular therapies to replace retinal pigmented epithelium (RPE) and / or photoreceptors to treat age-related macular degeneration (AMD), Stargardt's macular dystrophy, and retinitis pigmentosa are currently being developed. Over the past decade, significant advancements have been made using different types of

human stem cells with varying capacities to differentiate into these target retinal cell types. We review and evaluate pluripotent stem cells, both human embryonic stem cells and human induced pluripotent stem cells, as well as protocols for differentiation of ocular cells, and culture and transplant techniques that might be used to deliver cells to patients. J. Cell. Physiol. © 2011 Wiley-Liss, Inc.

PMID: 21520078 [PubMed - as supplied by publisher]

## Epidemiology & pathogenesis

**Ophthalmology. 2011 Apr 22. [Epub ahead of print]**

**Associations of Cigarette Smoking But Not Serum Fatty Acids with Age-related Macular Degeneration in a Japanese Population.**

Kabasawa S, Mori K, Horie-Inoue K, Gehlbach PL, Inoue S, Awata T, Katayama S, Yoneya S.

Department of Ophthalmology, Saitama Medical University, Iruma, Saitama, Japan.

PURPOSE: To assess modifiable environmental risk factors and protective factors for age-related macular degeneration (AMD) in a native Japanese population.

DESIGN: A case-control study.

PARTICIPANTS: We included 422 case-control samples composed of 279 consecutive AMD cases and 143 controls.

METHODS: Information regarding systemic conditions and lifestyle were documented in each subject by standardized questionnaire including age, gender, smoking history, body mass index (BMI), and history of cardiovascular disease, hypertension, and diabetes. Serum fatty acids profiles were analyzed by gas chromatography performed on blood samples taken from each study participant. Logistic regression and multiple comparison analyses were utilized in this study.

MAIN OUTCOME MEASURES: Population-specific information assessing systemic conditions, lifestyle, and serum fatty acid profiles.

RESULTS: Among environmental factors analyzed cigarette smoking showed the most significant association with development of all AMD ($P<0.00001$; odds ratio [OR], 4.06; 95% confidence interval [CI], 2.22-7.43), typical neovascular AMD ($P<0.0001$, OR, 4.59; 95% CI, 2.29-9.18), and polypoidal choroidal vasculopathy ($P<0.001$; OR, 4.87; 95% CI, 1.96-12.1). Hypertension and BMI showed a mild association with AMD. Although male prevalence was significantly higher in all case groups than in controls with conventional Scheffe correction, there was no association of gender with AMD development when logistic regression analysis was used to adjust for cigarette smoking. There was no difference in fatty acid profiles, except for a mild association of eicosapentaenoic acid concentration in the all AMD group.

CONCLUSIONS: In the Japanese population studied, cigarette smoking influenced the risk of AMD but fractionated serum fatty acid levels did not. Although prior reports indicate a male predominance in Japanese patients with AMD, this study demonstrates that cigarette smoking accounts for this confounding bias. In addition, our population-specific data do not demonstrate significant differences in serum fatty acid composition, including ω-3 and ω-6 long chain polyunsaturated fatty acids, in Japanese patients with and without AMD. These results are consistent with the high proportion of smokers in aged Japanese men and the high fish oil intake in this population. .

PMID: 21514959 [PubMed - as supplied by publisher]

**Am J Pathol. 2011 May;178(5):2416-23.**

**Interleukin-1β inhibition prevents choroidal neovascularization and does not exacerbate photoreceptor degeneration.**

Lavalette S, Raoul W, Houssier M, Camelo S, Levy O, Calippe B, Jonet L, Behar-Cohen F, Chemtob S, Guillonneau X, Combadière C, Sennlaub F.

INSERM, UMR S 872, Centre de Recherche des Cordeliers, Paris, France; UMR S 872, University Pierre and Marie Curie Paris 6, Paris, France; UMR S 872, Université Paris Descartes, Paris, France.

Abstract

The pro-inflammatory cytokine IL-1β has been shown to promote angiogenesis. It can have a neurotoxic or neuroprotective effect. Here, we have studied the expression of IL-1β in vivo and the effect of the IL-1 receptor antagonist on choroidal neovascularization (CNV) and retinal degeneration (RD). IL-1β expression significantly increased after laser injury (real time PCR) in C57BL/6 mice, in the C57BL/6 Cx3cr1(-/-) model of age-related macular degeneration (enzyme-linked immunoabsorbent assay), and in albino Wistar rats and albino BALB Cx3cr1(+/+) and Cx3cr1(-/-) mice (enzyme-linked immunoabsorbent assay) after light injury. IL-1β was localized to Ly6G-positive, Iba1-negative infiltrating neutrophils in laser-induced CNV as determined by IHC. IL-1 receptor antagonist treatment significantly inhibited CNV but did not affect Iba1-positive macrophage recruitment to the injury site. IL-1β significantly increased endothelial cell outgrowth in aortic ring assay independently of vascular endothelial growth factor, suggesting a direct effect of IL-1β on choroidal endothelial cell proliferation. Inhibition of IL-1β in light- and laser-induced RD models did not alter photoreceptor degeneration in Wistar rats, C57BL/6 mice, or RD-prone Cx3cr1(-/-) mice. Our results suggest that IL-1β inhibition might represent a valuable and safe alternative to inhibition of vascular endothelial growth factor in the control of CNV in the context of concomitant photoreceptor degeneration as observed in age-related macular degeneration.

PMID: 21514452 [PubMed - in process]

**Exp Eye Res. 2011 Apr 16. [Epub ahead of print]**

**Chemical composition of melanosomes, lipofuscin and melanolipofuscin granules of human RPE tissues.**

Biesemeier A, Schraermeyer U, Eibl O.

Institute of Applied Physics, University of Tuebingen, Auf der Morgenstelle 10, 72076 Tuebingen, Germany; University Eye Hospital, Schleichstr 12/1, 72076 Tuebingen, Germany.

Abstract

Energy-filtered analytical transmission electron microscopy was used to image the ultrastructure and determine quantitatively the chemical composition of pigment granules of the choroid and retinal pigment epithelium of two healthy human donors, aged 68 and 85 years. The electron microscopy preparation procedure did not affect the autofluorescence of melanolipofuscin and lipofuscin granules, since staining was omitted during sample preparation. Oval melanosomes, melanolipofuscin and lipofuscin granules were observed, having sizes of about 1.5μm×0.5μm, and analyzed using energy-dispersive X-ray microanalysis and electron energy loss spectroscopy. Up to now, these pigments could only be identified by scattering contrast in bright field images, with melanosomes having dark contrast and lipofuscin being much brighter. High-precision energy-dispersive X-ray microanalysis of pigment granules (>15,000 integrated counts in the oxygen K(α) peak) yielded minimum detectable mole fractions of about 0.02at% for copper and zinc. For the first time, quantitative analytical electron microscopy yielded the chemical composition of the different pigments without prior isolation from the tissue. This is important to better understand physical and chemical properties of the pigments and their metabolism and turnover. The composition of melanosomes

and lipofuscin can clearly be distinguished by the applied methods. Melanosomes were the pigments with largest oxygen (about 5at%) and nitrogen (about 10at%) mole fractions. The S/N ratio determination demonstrated a high pheomelanin content of the melanosomes. Lipofuscin had a significantly smaller oxygen mole fraction (about 4at%) and nitrogen was found to be only slightly above the limit of detection (0.4at%). For comparison, the cytoplasm contained oxygen and nitrogen mole fractions of 3at% and 0.8at%. Bright field images showed melanolipofuscin granules having a core-shell structure with a dark inner and a bright outer fraction. The dark fraction had a chemical composition close to the melanosomes and the composition of the bright fraction could be distinguished from that of lipofuscin due to a significantly increased nitrogen mole fraction in the melanolipofuscin granule. For all pigments observed the oxygen mole fraction yielded a positive correlation with the calcium mole fraction as previously established for melanosomes. Only lipofuscin contained measurable phosphorus mole fractions, which also correlated positively with oxygen. In lipofuscin, mole fractions of nitrogen were significantly smaller than in melanosomes and only indicated a small fraction of proteins. In contrast, the phosphorus mole fraction was significantly larger indicating the presence of significant amounts of phospholipids. Copper and zinc mole fractions were larger than 0.1at% in the melanosomes, but were below the detection limit in the lipofuscin granules. Compared to melanosomes of monkeys and rats analyzed beforehand, human retinal pigment epithelium melanosomes contained the highest amount of zinc, which even exceeded the calcium mole fraction. Trace elements like zinc are of great importance for metabolism and anti-oxidative mechanisms and also play a role in the progression of age related macular degeneration. They can now be investigated by quantitative analytical electron microscopy.

PMID: 21524648 [PubMed - as supplied by publisher]

**Arterioscler Thromb Vasc Biol. 2011 Apr 28. [Epub ahead of print]**

**Amyloid {beta} Enhances Migration of Endothelial Progenitor Cells by Upregulating CX3CR1 in Response to Fractalkine, Which May Be Associated With Development of Choroidal Neovascularization.**

Wang J, Ohno-Matsui K, Nakahama KI, Okamoto A, Yoshida T, Shimada N, Mochizuki M, Morita I.

Department of Ophthalmology and Visual Science and Section of Cellular Physiological Chemistry, Tokyo Medical and Dental University, Tokyo, Japan; Department of Obstetrics and Gynecology, Jikei University School of Medicine, Tokyo, Japan.

OBJECTIVE: Deposits that accumulate beneath retinal pigment epithelium, called drusen, are early signs of age-related macular degeneration (AMD). We have shown that amyloid β (Aβ) is present in drusen, and Aβ may be involved in AMD development. We have also shown that endothelial progenitor cells (EPCs) may contribute to the development of choroidal neovascularization (CNV). Thus, the purpose of this study was to investigate the role played by CX3CR1, a chemokine receptor, in EPC migration and CNV formation.

METHODS AND RESULTS: EPCs collected from human umbilical cords were found to express higher levels of CX3CR1 than human umbilical vein endothelial cells, and exposure of EPCs to Aβ caused further upregulation of CX3CR1. This upregulation was decreased by blocking fractalkine, a ligand of CX3CR1. Exposure of EPCs to fractalkine increased their migration, but pretreatment with Aβ enhanced the migration. The fractalkine-induced EPC migration was more inhibited by EPCs derived from CX3CR1(-/-) mice than wild-type mice. The area of laser-induced CNV was significantly smaller in wild-type mice that received bone marrow transplantation from CX3CR1(-/-) mice than in those that received transplantation from wild-type mice.

CONCLUSIONS: These data suggest that Aβ enhances EPC migration through the upregulation of CX3CR1. This upregulation might play a role in development of CNV.

PMID: 21527754 [PubMed - as supplied by publisher]

**Optometry. 2011 May;82(5):310-7.**

**Knowledge about the relationship between smoking and blindness in Canada, the United States, the United Kingdom, and Australia: results from the International Tobacco Control Four-Country Project.**

Kennedy RD, Spafford MM, Parkinson CM, Fong GT.

University of Waterloo, Waterloo, Ontario, Canada; Global Center for Tobacco Control, Harvard School of Public Health, Boston, Massachusetts.

PURPOSE: Smoking is causally associated with certain prevalent visually impairing eye diseases, including age-related macular degeneration and cataract. Studies have found that people are afraid of "going blind" and may be motivated to quit smoking if they know that vision loss is associated with smoking behavior.

METHODS: A random-digit dialed telephone survey was used to measure health knowledge of adult smokers in Canada (n = 2,765), the United States (n = 3,178), the United Kingdom (n = 2,767), and Australia (n = 2,623) as part of the International Tobacco Control Four-Country Project.

RESULTS: A low proportion of smokers from Canada (13.0%), the United States (9.5%), and the United Kingdom (9.7%) believed that smoking can cause blindness. In contrast, 47.2% of Australian smokers believed that smoking causes blindness. Australia was the only country during the sampling period to have national awareness campaigns about smoking and its effects on eye health.

CONCLUSION: These findings point to the need across countries to educate the public on this important consequence of smoking. There is an opportunity for the public health and eye health communities to work to educate the public about the impacts smoking has on eye health to improve quit rates and help discourage people from starting to smoke.

PMID: 21524603 [PubMed - in process]

**Cell Cycle. 2011 May 15;10(10). [Epub ahead of print]**

**The purpose of the HIF-1/PHD feedback loop: To limit mTOR-induced HIF-1α**

Demidenko ZN, Blagosklonny MV.

Department of Cell Stress Biology; Roswell Park Cancer Institute; Buffalo NY, USA.

Abstract

Prolyl hydroxylases (PHDs) target hypoxia-inducible factor-1a (HIF-1α) for degradation. Hypoxia inactivates PHDs, causing accumulation of HIF-1α. In turn, HIF-1 further trans-activates PHDs. The purpose of this feedback loop is thought to limit HIF-1α-accumulation caused by hypoxia. Here we suggest that the feedback is "intended" to limit the induction of HIF-1α by insulin, growth factors, hormones, cytokines and nutrients. These stimuli induce HIF-1α by increasing its translation, not by inhibiting PHDs. As exemplified herein, in a mTOR-dependent manner, insulin transiently induced HIF-1α in retinal pigment epithelial (RPE) cells. Induction of HIF-1α was followed by activation of HIF-dependent transcription. Furthermore, DFX, which inactivates PHDs, potentiated the induction of HIF-1α by insulin. We discuss that the most relevant function of the PHD-HIF feedback loop is to limit the induction of HIF-1α by mTOR. The failure to limit mTOR-dependent induction of HIF-1 may contribute to age-related macular degeneration and diabetic retinopathy, suggesting rapamycin for prevention of these age-related diseases.

PMID: 21521942 [PubMed - as supplied by publisher]

**ACS Chem Biol. 2011 Apr 26. [Epub ahead of print]**

**Synthesis and Activity of Thioether-containing Analogues of the Complement Inhibitor Compstatin.**

Knerr PJ, Tzekou A, Ricklin D, Qu H, Chen H, van der Donk WA, Lambris JD.

Abstract

Disulfide bonds are essential for the structural stability and biological activity of many bioactive peptides; however, these bonds are sensitive to reduction, which can limit the peptides' therapeutic utility. Substituting a disulfide bond with a cystathionine-based thioether bridge is an attractive means of preventing this reductive lability because it causes minimal structural alteration. We have now applied this approach to the therapeutic complement inhibitor compstatin, a disulfide-containing peptide currently in clinical trials for age-related macular degeneration, in an effort to maintain its potent activity while improving its biological stability. Thioether-containing compstatin analogues were produced via solid-phase synthesis, utilizing pre-formed, orthogonally protected cystathionine amino acids and on-resin cyclization. While the affinity of these compounds for their biological target and their potency in inhibiting complement activation were slightly lower than those of the parent peptides, the improved stability conferred by the thioether bond nevertheless makes this new class of compstatin peptides a promising alternative for therapeutic applications.

PMID: 21520911 [PubMed - as supplied by publisher]

## Genetics

**PLoS One. 2011 Apr 19;6(4):e19108.**

**Association between the SERPING1 Gene and Age-Related Macular Degeneration and Polypoidal Choroidal Vasculopathy in Japanese.**

Nakata I, Yamashiro K, Yamada R, Gotoh N, Nakanishi H, Hayashi H, Tsujikawa A, Otani A, Saito M, Iida T, Oishi A, Matsuo K, Tajima K, Matsuda F, Yoshimura N.

Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan.

PURPOSE: Recently, a complement component 1 inhibitor (SERPING1) gene polymorphism was identified as a novel risk factor for age-related macular degeneration (AMD) in Caucasians. We aimed to investigate whether variations in SERPING1 are associated with typical AMD or with polypoidal choroidal vasculopathy (PCV) in a Japanese population.

METHODS: We performed a case-control study in a group of Japanese patients with typical AMD (n=401) or PCV (n=510) and in 2 independent control groups-336 cataract patients without age-related maculopathy and 1,194 healthy Japanese individuals. Differences in the observed genotypic distribution between the case and control groups were tested using chi-square test for trend. Age and gender were adjusted using logistic regression analysis.

RESULTS: We targeted rs2511989 as the haplotype-tagging single nucleotide polymorphism (SNP) for the SERPING1 gene, which was reported to be associated with the risk of AMD in Caucasians. Although we compared the genotypic distributions of rs2511989 in typical AMD and PCV patients against 2 independent control groups (cataract patients and healthy Japanese individuals), SERPING1 rs2511989 was not significantly associated with typical AMD (P=0.932 and 0.513, respectively) or PCV (P=0.505 and 0.141, respectively). After correction for age and gender differences based on a logistic regression model, the difference in genotypic distributions remained insignificant (P>0.05). Our sample size had a statistical power of more than 90% to detect an association of a risk allele with an odds ratio reported in the original studies for rs2511989 for developing AMD.

CONCLUSIONS: In the present study, we could not replicate the reported association between SERPING1 and either neovascular AMD or PCV in a Japanese population; thus, the results suggest that SERPING1 does not play a significant role in the risk of developing AMD or PCV in Japanese.

PMID: 21526158 [PubMed - in process] Free Article

**BMC Med Genet. 2011 Apr 26;12(1):58. [Epub ahead of print]**

**Evaluation of variants in the selectin genes in age-related macular degeneration.**

Mullins RF, Skeie JM, Folk JC, Solivan-Timpe FM, Oetting TA, Huang J, Wang K, Stone EM, Fingert JH.

BACKGROUND: Age-related macular degeneration (AMD) is a common disease of the elderly that leads to loss of the central visual field due to atrophic or neovascular events. Evidence from human eyes and animal models suggests an important role for macrophages and endothelial cell activation in the pathogenesis of AMD. We sought to determine whether common ancestral variants in genes encoding the selectin family of proteins are associated with AMD.

METHOD: S Expression of E-selectin, L-selectin and P-selectin was examined in choroid and retina by quantitative PCR and immunofluorescence. Samples from patients with AMD (n=341) and controls (n=400) were genotyped at a total of 34 SNPs in the SELE, SELL and SELP genes. Allele and genotype frequencies at these SNPs were compared between AMD patients and controls as well as between subtypes of AMD (dry, geographic atrophy, and wet) and controls.

RESULTS: High expression of all three selectin genes was observed in the choroid as compared to the retina. Some selectin labeling of retinal microglia, drusen cores and the choroidal vasculature was observed. In the genetic screen of AMD versus controls, no positive associations were observed for SELE or SELL. One SNP in SELP (rs3917751) produced p-values < 0.05 (uncorrected for multiple measures). In the subtype analyses, 6 SNPs (one in SELE, two in SELL, and three in SELP) produced p-values < 0.05. However, when adjusted for multiple measures with a Bonferroni correction, only one SNP in SELP (rs3917751) produced a statistically significant p-value (p = 0.0029).

CONCLUSIONS: This genetic screen did not detect any SNPs that were highly associated with AMD affection status overall. However, subtype analysis showed that a single SNP located within an intron of SELP (rs3917751) is statistically associated with dry AMD in our cohort. Future studies with additional cohorts and functional assays will clarify the biological significance of this discovery. Based on our findings, it is unlikely that common ancestral variants in the other selectin genes (SELE and SELL) are risk factors for AMD. Finally, it remains possible that sporadic or rare mutations in SELE, SELL, or SELP have a role in the pathogenesis of AMD.

PMID: 21521525 [PubMed - as supplied by publisher]

## Diet

**J Cell Physiol. 2011 Aug;226(8):2025-32. doi: 10.1002/jcp.22532.**

**Modulation of oxidative stress responses in the human retinal pigment epithelium following treatment with vitamin C.**

Yin J, Thomas F, Lang JC, Chaum E.

Department of Ophthalmology, University of Tennessee Health Science Center, Memphis, Tennessee.

Abstract

Oxidative stress (OS) in the retina plays an important role in the development and progression of age-related macular degeneration (AMD). Our previous work has shown that OS can quantitatively regulate the expression of AP-1 family genes in the retinal pigment epithelium (RPE). In this study, we sought to determine whether AP-1 genes can be used as cellular biomarkers of OS to evaluate the efficacy of ascorbate, the major aqueous-phase antioxidant in the blood, in reducing OS in RPE cells in vitro. Human ARPE19 cells were pretreated with increasing levels of ascorbate (0-500 μM) for 3 days which was then removed from the medium. OS was induced 24 h later by the addition of hydrogen peroxide for 1-4 h, to bring the final media concentration of H(2) O(2) to 500 μM. FosB, c-Fos, and ATF3 gene expression was examined from 0 to 24 h after OS. Pretreatment with 200 μM ascorbate maximally reduced the transcriptional OS response of AP-1 genes by up to 87% after 1 and 4 h, compared to controls. One hundred micromolar of ascorbate provided a statistically significant, but far more modest effect. Ascorbate supplementation of 100-200 μM appears to strongly inhibit OS-induced activation of AP-1 in vitro, but pretreatment with higher levels of ascorbate conferred no additional advantage. These studies suggest that there are optimal levels of antioxidant supplementation to the RPE in vitro. Laboratory assays based upon transcription factor biomarkers may be useful to define beneficial molecular responses to new antioxidants, alternative dosing regimens, and to explore therapeutic efficacy in OS models in vitro. J. Cell. Physiol. 226: 2025-2032, 2011.

PMID: 21520054 [PubMed - in process]