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MD Research News

Issue 65

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This free weekly bulletin lists the latest published research articles on macular degeneration (MD) as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases. These articles were identified by a search using the key term “macular degeneration”.

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Drug treatment

Clin Ophthalmol. 2012;6:61-9. Epub 2012 Jan 10.

The effect of intravitreal anti-VEGF agents on peripheral wound healing in a rabbit model.

Christoforidis J, Ricketts R, Pratt C, Pierce J, Bean S, Wells M, Zhang X, La Perle K.

College of Medicine, The Ohio State University, Columbus, OH, USA.

PURPOSE: To investigate the effect of intravitreal pegaptanib, bevacizumab, and ranibizumab on blood-vessel formation during cutaneous wound healing in a rabbit model and to compare this effect to placebo controls.

METHODS: Forty New Zealand albino rabbits underwent full thickness cutaneous wounds using 6-mm dermatologic punch biopsies. The rabbits were assigned to four groups of ten, each receiving intravitreal injections of pegaptanib, bevacizumab, ranibizumab, or no injection (untreated controls). Five rabbits from each group underwent wound harvesting on day 7 and five from each group on day 14. The skin samples were stained with hematoxylin and eosin (HE), Masson's trichrome (MT), and CD34 for vascular endothelial cells. Semiquantitative evaluation of HE- and MT-stained slides was performed by one pathologist. Quantitative assessment of mean neovascularization (MNV) scores was obtained from five contiguous biopsy margin 400× fields of CD34-stained sections by four independent observers.

RESULTS: Week 1 MNV scores in CD-34 stained sections were: untreated controls: 11.51 ± 4.36; bevacizumab: 7.41 ± 2.82 (P = 0.013); ranibizumab: 8.71 ± 4.08 (P = 0.071); and pegaptanib: 10.15 ± 5.59 (P = 0.378). Week 2 MNV data were: untreated controls: 6.14 ± 2.25; bevacizumab: 7.25 ± 2.75 (P = 0.471); ranibizumab: 4.53 ± 3.12 (P = 0.297); and, pegaptanib: 6.35 ± 3.09 (P = 0.892). Interobserver variability using intraclass correlation coefficient was 0.961.

CONCLUSIONS: At week 1, all three anti-VEGF agents had suppressed MNV scores compared to controls. Although not statistically significant, there was an inhibitory trend, particularly with bevacizumab and ranibizumab. These effects were diminished at 2 weeks, reflecting a transition between the proliferative and remodeling phases of wound healing.

PMID: 22275809 [PubMed - in process] PMCID: PMC3261691

Retina. 2012 Jan 19. [Epub ahead of print]

TREATMENT OF NONNEOVASCULAR IDIOPATHIC MACULAR TELANGIECTASIA TYPE 2 WITH INTRAVITREAL RANIBIZUMAB: Results of a Phase II Clinical Trial.

Toy BC, Koo E, Cukras C, Meyerle CB, Chew EY, Wong WT.

*Division of Epidemiology and Clinical Applications †Office of the Scientific Director, National Eye Institute, National Institutes of Health, Bethesda, MD.

PURPOSE: To evaluate the safety and preliminary efficacy of intravitreal ranibizumab for nonneovascular idiopathic macular telangiectasia Type 2.

METHODS: Single-center, open-label Phase II clinical trial enrolling five participants with bilateral nonneovascular idiopathic macular telangiectasia Type 2. Intravitreal ranibizumab (0.5 mg) was administered every 4 weeks in the study eye for 12 months with the contralateral eye observed. Outcome measures included changes in best-corrected visual acuity, area of late-phase leakage on fluorescein angiography, and retinal thickness on optical coherence tomography.

RESULTS: The study treatment was well tolerated and associated with few adverse events. Change in best -corrected visual acuity at 12 months was not significantly different between treated study eyes (0.0 ± 7.5 letters) and control fellow eyes (+2.2 ± 1.9 letters). However, decreases in the area of late-phase fluorescein angiography leakage (-33 ± 20% for study eyes, +1 ± 8% for fellow eyes) and in optical coherence tomography central subfield retinal thickness (-11.7 ± 7.0% for study eyes and -2.9 ± 3.5% for fellow eyes) were greater in study eyes compared with fellow eyes.

CONCLUSION: Despite significant anatomical responses to treatment, functional improvement in visual acuity was not detected. Intravitreal ranibizumab administered monthly over a time course of 12 months is unlikely to provide a general and significant benefit to patients with nonneovascular idiopathic macular telangiectasia Type 2.

PMID: 22266930 [PubMed - as supplied by publisher]

Ann Pharmacother. 2012 Jan 24. [Epub ahead of print]

Bevacizumab for the Treatment of Neovascular Age-Related Macular Degeneration (February).

Pitlick JM, Vecera KF, Barnes KN, Reski JW, Forinash AB.

< St. Louis College ofPharmacy, St. Louis, MO.

OBJECTIVE: To review data regarding the efficacy and safety of bevacizumab for the treatment of neovascular age-related macular degeneration (nARMD).

DATA SOURCES: Literature was searched using MEDLINE (1976-September 2011) and EMBASE (1973-September 2011). Search terms included bevacizumab, Avastin, neovascular macular degeneration, age-related macular degeneration, vascular endothelial growth factor, intravitreal, and safety. Reference citations were reviewed for relevant information.

STUDY SELECTION AND DATA EXTRACTION: All randomized clinical trials published in English with data assessing the safety and efficacy of bevacizumab for nARMD were evaluated.

DATA SYNTHESIS: The only Food and Drug Administration-approved treatments for nARMD are photodynamic therapy (PDT) with verteporfin, intravitreal pegaptanib, and ranibizumab. However, bevacizumab has gained attention as a potential agent in treating nARMD and is now widely used in practice. PDT with verteporfin and pegaptanib has shown only stabilization of visual acuity (VA). When the efficacy of bevacizumab was compared to these therapies, bevacizumab clinically and statistically improved VA outcomes. When compared to ranibizumab, which has also been shown to improve VA, bevacizumab showed no significant difference in VA outcomes and was associated with a decrease in average annual cost of $22,805.

CONCLUSIONS: Bevacizumab administered intravitreally is appropriate for prevention of vision loss and recovery of VA in patients with nARMD. Although further analysis of long-term effects of bevacizumab on

VA and safety is needed, it is potentially a more cost-effective option than ranibizumab for the treatment of nARMD.

PMID: 22274144 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2012 Jan 26. doi: 10.1111/j.1755-3768.2011.02262.x. [Epub ahead of print]

Ranibizumab in South Korean and Taiwanese patients with age-related macular degeneration: primary outcome of the EXTEND III study.

Lee FL, Kwon OW, Chung H, Lai CC, Sheu SJ, Yoon YH; on behalf of the EXTEND III Study Group.

Taipei Veterans General Hospital, Taipei, Taiwan The Retina Center, Nune Eye Hospital, Seoul, Korea Department of Ophthalmology, Seoul National University Hospital, Seoul, Korea Chang-Gung Memorial Hospital, Lin-Ko, Taiwan Kaohsiung Veterans General Hospital, Kaohsiung, National Yang-Ming University, Taipei, Taiwan Department of Ophthalmology, Asan Medical Center, College of Medicine, University of Ulsan, Seoul, Korea.

PMID: 22280368 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2012 Jan 23. doi: 10.1111/j.1755-3768.2011.02327.x. [Epub ahead of print]

Same-day consecutive bilateral intravitreal injections of ranibizumab for the treatment of bilateral active choroidal neovascularization in age-related macular degeneration.

Shah M, Amoaku WM.

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

PMID: 22269064 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2012 Jan 23. doi: 10.1111/j.1755-3768.2011.02282.x. [Epub ahead of print]

Resolution of diabetic papillopathy after a single intravitreal injection of ranibizumab.

Willerslev A, Munch IC, Larsen M.

Department of Ophthalmology, Glostrup Hospital, Glostrup, Denmark Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark.

PMID: 22268957 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Lancet. 2012 Jan 24. [Epub ahead of print]

Embryonic stem cell trials for macular degeneration: a preliminary report.

Schwartz SD, Hubschman JP, Heilwell G, Franco-Cardenas V, Pan CK, Ostrick RM, Mickunas E, Gay R, Klimanskaya I, Lanza R.

Jules Stein Eye Institute Retina Division, Department of Ophthalmology, David Geffen School of Medicine, University of California, Los Angeles, CA, USA.

BACKGROUND: It has been 13 years since the discovery of human embryonic stem cells (hESCs). Our report provides the first description of hESC-derived cells transplanted into human patients.

METHODS: We started two prospective clinical studies to establish the safety and tolerability of subretinal transplantation of hESC-derived retinal pigment epithelium (RPE) in patients with Stargardt's macular dystrophy and dry age-related macular degeneration-the leading cause of blindness in the developed world. Preoperative and postoperative ophthalmic examinations included visual acuity, fluorescein angiography, optical coherence tomography, and visual field testing. These studies are registered with ClinicalTrials.gov, numbers NCT01345006 and NCT01344993.

FINDINGS: Controlled hESC differentiation resulted in greater than 99% pure RPE. The cells displayed typical RPE behaviour and integrated into the host RPE layer forming mature quiescent monolayers after transplantation in animals. The stage of differentiation substantially affected attachment and survival of the cells in vitro after clinical formulation. Lightly pigmented cells attached and spread in a substantially greater proportion (>90%) than more darkly pigmented cells after culture. After surgery, structural evidence confirmed cells had attached and continued to persist during our study. We did not identify signs of hyperproliferation, abnormal growth, or immune mediated transplant rejection in either patient during the first 4 months. Although there is little agreement between investigators on visual endpoints in patients with low vision, it is encouraging that during the observation period neither patient lost vision. Best corrected visual acuity improved from hand motions to 20/800 (and improved from 0 to 5 letters on the Early Treatment Diabetic Retinopathy Study [ETDRS] visual acuity chart) in the study eye of the patient with Stargardt's macular dystrophy, and vision also seemed to improve in the patient with dry age-related macular degeneration (from 21 ETDRS letters to 28).

INTERPRETATION: The hESC-derived RPE cells showed no signs of hyperproliferation, tumorigenicity, ectopic tissue formation, or apparent rejection after 4 months. The future therapeutic goal will be to treat patients earlier in the disease processes, potentially increasing the likelihood of photoreceptor and central visual rescue.

FUNDING: Advanced Cell Technology.

PMID: 22281388 [PubMed - as supplied by publisher]

Int Ophthalmol. 2012 Jan 25. [Epub ahead of print]

The relationship between optical coherence tomography patterns, angiographic parameters and visual acuity in age-related macular degeneration.

Yaylali SA, Akcakaya AA, Erbil HH, Candemir B, Mesci C, Acar H.

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Abstract

To assess the relationships between visual acuity (VA), fluorescein angiographic parameters and optical coherence tomography (OCT) patterns in exudative age-related macular degeneration (AMD). Fifty eyes with confirmed diagnosis of new exudative AMD who underwent fluorescein angiography (FA) and OCT evaluation were reviewed retrospectively. The greatest linear diameter of lesion (GLD) by FA and central foveal thickness (CFT) by OCT were measured. The OCT scans were evaluated for the presence of diffuse retinal thickening (D), cystic spaces (C), subretinal fluid (S) and pigment epithelial detachment (P) and five OCT patterns were detected (D + S; C; C + S; P + C + S; P + D + S). Angiographic classification of choroidal neovascularizations was performed. Correlations were statistically significant for VA and CFT in all patients whereas VA and GLD correlation was statistically significant only in predominantly classic and minimal classic lesions. The lowest VA values were detected in patients with COCT pattern and/or predominantly classic lesion type by FA. The OCT and FA findings when evaluated simultaneously may provide information regarding visual function in AMD.

PMID: 22274757 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2012 Jan 23. doi: 10.1111/j.1755-3768.2011.02331.x. [Epub ahead of print]

Multimodal imaging of dry age-related macular degeneration.

Forte R, Querques G, Querques L, Massamba N, Le Tien V, Souied EH.

Department of Ophthalmology, Intercommunal Hospital of Creteil, University Paris XII, France.

Purpose: The purpose of this study was to understand clinical significance of near-infrared reflectance (NIR), blue fundus autofluorescence (FAF) and near-infrared autofluorescence (NIA) in dry age-related macular degeneration (AMD), by correlation with fluorescein angiography (FA) and cross-sectional spectral domain optical coherence tomography (SD OCT).

Methods: We evaluated 110 eyes (62 patients, mean age: 64 ± 8 years) diagnosed with dry AMD between January 2010 and December 2010, which underwent NIR (λ = 830 nm), FAF and FA (excitation λ = 488 nm; emission λ > 500 nm), NIA (excitation λ = 787 nm; emission λ > 800 nm), and simultaneous SD OCT scanning using a combined confocal scanning laser ophthalmoscope/SD OCT device (Spectralis HRA + OCT; Heidelberg Engineering, Heidelberg, Germany).

Results: Drusen showed variable increased/decreased NIR, FAF, NIA and FA, which corresponded to variable increased/decreased thickness of the retinal pigment epithelium (RPE) and possible presence of subretinal deposits on SD OCT. Geographic atrophy (GA) was present in 43/110 eyes (39.0%) and showed increased NIR and fluorescence (FA), absent FAF and NIA, and loss of RPE on SD OCT. The hyperautofluorescence of the GA margin was never larger in FAF than that in NIA, while in 16.2% of cases, it was larger in NIA than that in FAF and corresponded to mild choroidal hyperreflectivity on SD OCT.

Conclusions: Simultaneous recording of SD OCT scans provided ultrastructural data for the evaluation of NIR, FAF, NIA and FA in dry AMD. Near-infrared autofluorescence might detect earlier than FAF areas of RPE cell loss at the GA margin.

PMID: 22269083 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2012 Jan 26.

Assessment of Differential Pharmacodynamic Effects using Optical Coherence Tomography in Neovascular Age-Related Macular Degeneration.

Keane PA, Heussen FM, Ouyang Y, Mokwa N, Walsh AC, Tufail A, Sadda SR, Patel PJ.

NIHR Biomedical Research Centre for Ophthalmology, Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology.

Purpose: To assess the differential pharmacodynamic effects of bevacizumab (Avastin), pegaptanib (Macugen), and verteporfin photodynamic therapy (PDT), using novel OCT parameters, in a recently completed phase III/IV clinical trial.

Methods: Data from 122 patients participating in the Avastin (Bevacizumab) for Choroidal neovascularization (ABC) trial, were evaluated. Stratus OCT images were analyzed using custom software - changes in volume of the neurosensory retina, subretinal fluid (SRF), pigment epithelium detachment (PED), and subretinal tissue, were calculated over the 54-week trial period.

Results: Reductions in retinal oedema were more than twice as great from bevacizumab than pegaptanib (-0.82 mm(3) versus -0.31 mm(3)), while SRF reduction was more than three times greater (-0.54 mm(3) versus -0.15 mm(3)). Both bevacizumab and pegaptanib led to rapid reductions in subretinal tissue; however, in those receiving pegaptanib, these improvements were not maintained (at week 54: -0.22 mm (3) versus +0.18 mm(3)). Acute increases in SRF were seen one week after PDT (+0.36 mm(3)) and, across all treatment groups, PED volume tended to remain unchanged, or regress only slowly.

Conclusions: In clinical trials, quantitative OCT subanalysis increases the amount of clinically useful information that can be obtained from OCT images. In the emerging era of neovascular AMD therapeutics, the capacity of OCT to provide such detailed pharmacodynamic information, in a non-invasive manner, is likely to attain increased importance. In future comparative studies, evaluation of subretinal tissue may highlight differential effects on vascular proliferation, while measurement of PED volume may prove useful for the estimation of retinal and sub-retinal pigment epithelium (RPE) therapeutic penetration.

PMID: 22281826 [PubMed - as supplied by publisher]

Optom Vis Sci. 2012 Jan 19. [Epub ahead of print]

Fixation Patterns in Maculopathy: From Binocular to Monocular Viewing.

Tarita-Nistor L, Brent MH, Steinbach MJ, González EG.

*PhD †MD, FRCSC Vision Science Research Program, Toronto Western Hospital, Toronto, Ontario, Canada (LT-N, MHB, MJS, EGG), Centre for Vision Research, York University, Toronto, Ontario, Canada (LT-N, MJS, EGG), and Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, Ontario, Canada (LT-N, MHB, MJS, EGG).

PURPOSE: The goal of this study was to explore binocular coordination during fixation in patients with age-related macular degeneration (AMD) and to investigate whether there is a shift in eye position when the viewing condition changes from binocular to monocular.

METHODS: Sixteen people with normal vision and 12 patients with AMD were asked to look at a 3 deg fixation target with both eyes and with each eye individually while the fellow eye was covered by an infrared filter. Fixational eye movements were recorded for both eyes with an EyeLink eye-tracker in all conditions. The shift in eye position at the end of every fixation period was calculated for each eye.

RESULTS: All people with normal vision as well as the majority of patients had good binocular coordination during fixation in the binocular viewing condition. When the viewing condition changed from binocular to monocular, three patients (25%) had atypical shifts in their eye position. The shift was related to (1) loss of fixational control when the better eye was covered and the worse eye viewed the target or (2) a slow drift of the viewing eye that was associated with a large phoria in the covered eye.

CONCLUSIONS: Patients with AMD have good binocular ocular motor coordination during fixation. A change in viewing condition from binocular to monocular can lead to disturbances in ocular motor control for some patients, especially in the worse eye.

PMID: 22266814 [PubMed - as supplied by publisher]

Value Health. 2012 Jan;15(1):118-27. Epub 2011 Oct 1.

A review of generic preference-based measures of health-related quality of life in visual disorders.

Tosh J, Brazier J, Evans P, Longworth L.

Health Economics and Decision Science, School of Health and Related Research, University of Sheffield, Sheffield, South Yorkshire, UK.

OBJECTIVE: This review examines generic preference-based measures and their ability to reflect health-related quality of life in patients with visual disorders.

METHODS: A systematic search was undertaken to identify clinical studies of patients with visual disorders where health state utility values were measured and reported. Data were extracted to assess the validity and responsiveness of the measures. A narrative synthesis of the data was undertaken due to the heterogeneity between different studies.

RESULTS: There was considerable heterogeneity in the 31 studies identified in terms of patient characteristics, visual disorders, and outcomes reported. Vision loss was associated with a reduction in scores across the preference-based measure, but the evidence on validity and responsiveness was mixed. The EQ-5D health-related assessment instrument's performance differed according to condition, with poor performance in age-related macular degeneration (AMD) and diabetic retinopathy. The more limited evidence on the HUI-3 instrument found it performed best in differentiating between severity groups of patients with glaucoma, AMD, cataracts, and diabetic retinopathy. One study reported data on the SF-6D instrument and showed it was able to differentiate between patients with AMD.

CONCLUSIONS: The performance of the EQ-5D in visual disorders was mixed. The HUI-3 seemed to perform better in some conditions, but the evidence on this and SF-6D is limited. More head to head comparisons of these three measures are required. The new five-level version of EQ-5D may do better at the milder end of visual function.

PMID: 22264979 [PubMed - in process]

Nurs Stand. 2011 Nov 9-15;26(10):23.

Success in sight.

Gould M.

Abstract

Staff working for a macular disease service in a London eye hospital have won an award for their work in providing a one-stop service.

PMID: 22206168 [PubMed - indexed for MEDLINE]

Patol Fiziol Eksp Ter. 2011 Jul-Sep;(3):16-20.

[Experimental study of safety in application of the Iris Medical IQ 810 diode laser in clinical treatment of age-related macular degeneration].

[Article in Russian]

[No authors listed]

During the study of diode laser radiation effect in micropulse mode on culture cells of human retinal pigment epithelium it was revealed that the quota of dead cells was a minimum. Besides, a certain conformity between dead cells quota and parameter characteristics of laser radiation. Based on the performed experimental study it was revealed that for a work using the Iris Medical IQ 810 diode laser in the micropulse mode following parameters: duration of pulse set--300ms, duration of function--9.1%, power--750mW are safe for retinal pigment epithelium cells. Rationales of safety in application of the infrared diode laser radiation in micropulse mode in clinic for treatment of age-related macular degeneration (AMD) exampled by cell culture of human retinal pigment epithelium.

PMID: 22279734 [PubMed - in process]

Acta Ophthalmol. 2012 Jan 26. doi: 10.1111/j.1755-3768.2011.02329.x. [Epub ahead of print]

Polypoidal choroidal vasculopathy in patients diagnosed with neovascular age-related macular degeneration in Denmark.

Ilginis T, Ottosen S, Harbo Bundsgaard K, Uggerhøj Andersen C, Vorum H.

Department of Ophthalmology, Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark.

PMID: 22280465 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2012 Jan 23. doi: 10.1111/j.1755-3768.2011.02352.x. [Epub ahead of print]

Failure to Detect an Effect of Pneumatic Displacement in the Management of Submacular Haemorrhage Secondary to Age-related Macular Degeneration: A Retrospective Case Series.

Hesgaard HB, Torkashvand M, la Cour M.

Department of Ophthalmology, University of Copenhagen, Glostrup Hospital, Denmark.

PMID: 22268661 [PubMed - as supplied by publisher]

Pathogenesis

Mol Vis. 2012;18:114-20. Epub 2012 Jan 17.

Hypoxia initiates sirtuin1-mediated vascular endothelial growth factor activation in choroidal endothelial cells through hypoxia inducible factor-2α.

Balaiya S, Khetpal V, Chalam KV.

University of Florida College of Medicine, Department of Ophthalmology Jacksonville, FL.

PURPOSE: Hypoxia is a critical pathological factor in a variety of retinal diseases, including age-related macular degeneration. It upregulates angiogenic growth factors and promotes neovascularization. Hypoxia changes the cellular redox state and activates class III histone deacetylase sirtuin1 (SIRT1). Activated SIRT1 signals hypoxia inducible factor (HIF)-2α, which transactivates vascular endothelial growth factor (VEGF) and erythropoietin. In this study, we investigated the role of hypoxia induced SIRT1 in choroidal neovascularization in relation to age-related macular degeneration.

METHODS: Choroidal endothelial cells (RF/6A) were maintained in a semiconfluent state and hypoxia was induced by exposing the cells to cobalt chloride for 24 h. Induction of hypoxia was confirmed by flow cytometric analysis and the levels of SIRT1 were noted in a hypoxic condition as well in the cells after blocking SIRT1 activity using sirtinol. The role of SIRT1 in the activation of HIF-2α and nuclear factor-κB (RelA/p65) during hypoxia in the presence or absence of SIRT1 was assessed using immunoblot analysis. VEGF levels were quantified using enzyme-linked immunosorbent assay.

RESULTS: Hypoxic induction was confirmed using flow cytometric analysis, which showed cell cycle arrest starting at a 200 μM concentration of cobalt chloride. Hypoxic treatment (200 μM concentration of cobalt chloride) increased SIRT1 levels to 7.8%, which reduced to control level after its activity was inhibited ($p<0.05$). Activated SIRT1 mediates HIF-2α and nuclear factor-κB (RelA/p65) expression to 4.5 fold and fivefold, respectively, compared to control, and the levels were suppressed following sirtinol treatment (4.1% and 39.3% respectively; $p=0.01$). Hypoxic treatment increased VEGF levels by 94.9±19.6 pg/ml compared to control levels (25.58±3.58 pg/ml). These levels decreased to 10.29±0.2 pg/ml after blocking SIRT1 activity using sirtinol, compared to control ($p<0.01$).

CONCLUSIONS: Our study results demonstrate that hypoxia mimetic cobalt chloride induces SIRT1 and augments HIF-2α, which activates and releases VEGF.

PMID: 22275802 [PubMed - in process] PMCID: PMC3265172

Mol Vis. 2012;18:103-13. Epub 2012 Jan 17.

Accumulation and autofluorescence of phagocytized rod outer segment material in macrophages and microglial cells.

Lei L, Tzekov R, Tang S, Kaushal S.

PURPOSE: To explore the ability of macrophages and microglial cells to phagocytize rod outer segments (ROSs) in a cell culture and characterize the resulting lipofuscin-like autofluorescence (LLAF).

METHODS: Either regular or modified ROSs or ROS components (11-cis-retinal, all-trans-retinal, lipids) were fed to macrophages and microglial cells for 4 days. Afterwards, autofluorescence was detected by fluorescence-activated cell sorting (FACS) at two different wavelengths (533 nm and 585 nm), and the cells were imaged by confocal and electron microscopy. Fluorescein isothiocyanate (FITC)-labeled ROSs were added to macrophage and microglial cell cultures for 1-24 h to determine the kinetics of phagocytosis in these cell lines.

RESULTS: Feeding with different ROSs or ROS components led to a significant increase in LLAF in both microglia and macrophages. The 4-hydroxynonenal (HNE)-modified ROSs gave rise to the highest increase in LLAF at both 533 nm and 585 nm. Application of 11-cis-retinal or all-trans-retinal resulted in higher LLAF at 585 nm, compared to application of 9-cis-retinal or liposomes. Fluorescein isothiocyanate-labeled ROSs co-localized well with lysosomes in both types of cells. HNE-modified ROSs were phagocytized more rapidly by both types of cells, compared to unmodified ROSs. Electron microscopy demonstrated inclusion bodies containing whorls of membranes in all types of cells fed with ROSs.

CONCLUSIONS: Both macrophages and microglia have the ability to phagocytize ROSs, and this results in increased autofluorescence. Oxidation of ROSs results in faster phagocytosis, higher levels of LLAF, and the appearance of more inclusion bodies inside the cells. Results from the present study suggest that both types of cells accumulate lipofuscin-like material under physiologically relevant conditions. Such accumulation could interfere with their ability to clear cellular debris and could be part of the pathogenetic mechanism for age-related macular degeneration and other lipofuscinopathies.

PMID: 22275801 [PubMed - in process] PMCID: PMC3265176

Pharmaceuticals (Basel). 2011 Dec;4(12):1551-1577.

Proteolytically Derived Endogenous Angioinhibitors Originating from the Extracellular Matrix.

Boosani CS, Sudhakar YA.

Cell Signaling, Retinal and Tumor Angiogenesis Laboratory, Department of Genetics, Boys Town National Research Hospital, Omaha, NE 68131, USA; ChandraShekhar.Boosani@boystown.org.

Abstract

Angiogenesis, a neovascularization process induced from the existing parent blood vessels, is a prerequisite for many physiological and pathological conditions. Under physiological conditions it is regulated by a balance between endogenous angioinhibitors and angioactivators, and an imbalance between them would lead to pathological conditions such as cancer, age-related macular degeneration (AMD), diabetic retinopathy, cardiovascular diseases, etc. Several proteolytically generated endogenous molecules have been identified which exhibit angioinhibition and/or antitumor activities. These angioinhibitors interact with endothelial and tumor cells by binding to distinct integrins and initiate many of their intracellular signaling mechanisms regulating the cell survival and or apoptotic pathways. The present review will focus on the extracellular matrix derived angioinhibitors, and their mechanisms of actions that point to the clinical significance and therapeutic implications.

PMID: 22267953 [PubMed] PMCID: PMC3260939

Epidemiology

Acta Ophthalmol. 2012 Jan 23. doi: 10.1111/j.1755-3768.2011.02316.x. [Epub ahead of print]

Associations of early age-related macular degeneration with ocular and general parameters. The central India eyes and medical study.

Jonas JB, Nangia V, Kulkarni M, Gupta R, Khare A.

Suraj Eye Institute, Nagpur, Maharashtra, India Department of Ophthalmology, Medical Faculty Mannheim of the Ruprecht-Karls-University Heidelberg, Mannheim, Germany.

Purpose: To assess associations between age-related macular degeneration (AMD) and ocular and general parameters. Methods: The Central India Eye and Medical Study, a population-based study performed in rural Central India, included 4711 subjects (aged 30+ years) out of 5885 eligible subjects (response rate: 80.1%). Fundus photographs were assessed using the Wisconsin Age-Related Maculopathy Grading system. Results: Fundus photographs were available for 4542 (96.4%) subjects. Early AMD was present in 215/4542 subjects (4.7 ± 0.3%), and late AMD was detected in 8/4542 (0.2 ± 0.03%) subjects. After adjustment for age, prevalence of AMD was significantly associated with hyperopic refractive error (p = 0.001), shorter axial length (p = 0.01), and higher corneal refractive power (p = 0.02). Each dioptre increase in hyperopic refraction or each millimetre decrease in axial length was associated with a 15% [odds ratio (OR):1.15; 95% confidence interval (CI): 1.06, 1.24] and 19% (OR: 0.81; 95%CI: 0.69, 0.95) increased probability of early AMD, respectively. AMD was not significantly associated with blood pressure, serum concentration of cholesterol, glycosylated haemoglobin Hb1Ac, high-density lipoproteins and postprandial glucose, gender, level of education, any parameter of smoking, alcohol consumption, psychiatric depression or of daily activities, anterior chamber depth, lens thickness, intraocular pressure, size of the optic disc, neuroretinal rim and parapapillary atrophy, nor amount of nuclear cataract and status after cataract surgery. If the statistical analysis was adjusted for age and refractive error, age-related macular degeneration was marginally significantly associated with a low intake of fruits (p = 0.06). Conclusions: Hyperopia (and short axial length) besides age was the single most important associated factor for AMD in adult Indians.

PMID: 22269029 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2012 Feb;153(2):214-221.e1.

Time trends in the incidence and causes of blindness in Israel.

Skaat A, Chetrit A, Belkin M, Kinori M, Kalter-Leibovici O.

Goldschleger Eye Institute, Sheba Medical Center, Tel Aviv University, Tel Hashomer, Israel.

PURPOSE: To evaluate time trends in the incidence and causes of new cases of blindness in Israel between 1999 and 2008.

DESIGN: Descriptive, retrospective population-based study.

METHODS: During the decade of the study, 19 862 inhabitants of Israel were newly registered as legally blind. Data were retrieved from the 1999 to 2008 annual reports of the National Registry of the Blind in Israel and were reviewed retrospectively. Specific rates by age, gender, calendar year, and cause of blindness were calculated. Total and cause-specific annual age-standardized rates were calculated as well. Findings were evaluated by the use of Poisson regression models.

RESULTS: The age-standardized rate of incidence of newly registered legal blindness at the end of the studied decade was half of that at the beginning, declining from 33.8 per 100 000 in 1999 to 16.6 per 100 000 in 2008. The decline mainly was attributable to a decreased incidence of blindness resulting from age-related macular degeneration, glaucoma, diabetic retinopathy, and cataract.

CONCLUSIONS: Contemporary interventions in ophthalmology combined with widely available universal free access to healthcare seem to be effective in causing a major reduction in the incidence of blindness.

PMID: 22264945 [PubMed - in process]

Am J Ophthalmol. 2012 Feb;153(2):209-213.e2.

Incidence of legal blindness from age-related macular degeneration in Denmark: year 2000 to 2010.

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PURPOSE: To report incidence rates of legal blindness from age-related macular degeneration (AMD) and other causes in Denmark from years 2000 to 2010 in the age group at risk of AMD aged 50 years and older.

DESIGN: Population-based observational registry study.

METHODS: settings: Membership register of the Danish Association of the Blind, the primary admission criterion of which is best-corrected visual acuity 0.1 (20/200) or lower in a person's better-seeing eye. study population: A total of 11 848 incident cases of legal blindness from a population of citizens aged ≥50 years numbering 1.71 million in 2000 and 1.87 million in 2010 with free access to a single-payer public health care system. main outcome measures: Incidence rates of legal blindness from AMD from 2000 to 2010.

RESULTS: The incidence rate of legal blindness attributable to AMD in citizens aged ≥50 years decreased from 52.2 cases per year per 100 000 in 2000 to 25.7 cases per year per 100 000 in 2010, corresponding to a reduction of 50% (95% confidence interval [CI(95)]: 45%-56%, P < .0001, adjusted for age), the bulk of the reduction occurring after 2006. The incidence of legal blindness from causes other than AMD decreased by 33% (CI(95): 21%-44%, P < .0001), most of the reduction occurring between 2000 and 2006.

CONCLUSION: From 2000 to 2010 the incidence of legal blindness from AMD fell to half the baseline incidence. The bulk of the reduction occurred after the introduction of intravitreally injected inhibitors of vascular endothelial growth factor in 2006.

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Prevalence of age-related macular degeneration in persons aged 90 years and older in Cologne.

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Genetics

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Association of polymorphisms in C2, CFB and C3 with exudative age-related macular degeneration in a Korean population.

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Abstract

This study was to investigate the association of genetic polymorphisms in complement component 2 (C2), complement factor B (CFB) and complement component 3 (C3) with exudative age-related macular degeneration (AMD) in a Korean population and the gene-gene and gene-environment interactions in the development of AMD. A total of six SNPs that are located in the C2 (rs547154, rs9332739), CFB (rs4151667, rs641153) and C3 (rs1047286, rs2230199) genes were genotyped in 350 samples comprised of 153 cases, 197 controls. The risk allele frequencies for rs547154 in C2 were 6.54% and 8.12% in AMD patients and controls. Those for rs641153 in CFB were 6.54% and 8.63% in AMD patients and controls. The risk allele frequency for rs9332739 in C2 (AMD, 0.65%, control, 2.03%) and rs4151667 in CFB (AMD, 0.65%, control, 1.78%) was very low. The protective allele of four SNPs was not significantly associated with decreased risk for AMD (p = 0.427, p = 0.199, p = 0.312, p = 0.303, respectively). The homozygotes for the protective allele of four SNPs were not significantly associated with decreased risk for AMD (p = 0.324, p = 0.474, p = 0.309, p = 0.411, respectively). The genetic effect of two SNPs in C3 could not be investigated because the variants were not observed. There was no evidence to support an interaction of these SNPs with LOC387715/HTRA1 variants or with environmental exposure like smoking. In conclusion, the genetic effect of C2, CFB and C3 polymorphisms, which are known to be important for AMD in Caucasian, were not significant in the Korean population. The low minor allele frequency of these SNPs in Koreans might have affected the results of this study. Ethnic differences in the roles of C2, CFB and C3 in conferring a risk of AMD should be further investigated.

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The association of CD36 variants with polypoidal choroidal vasculopathy compared to typical neovascular age-related macular degeneration.

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PURPOSE: To clarify the association of cluster of differentiation 36 (CD36) variants with polypoidal choroidal vasculopathy (PCV) and compare them with those in typical neovascular age-related macular degeneration (tAMD).

METHODS: We included 349 Japanese AMD patients (210 PCV, 139 tAMD) and 198 age-matched controls. Four tag single-nucleotide polymorphisms (SNPs)-rs10499862, rs3173798, rs3211883, and rs3173800-in the CD36 region were genotyped using the TaqMan assay. Allelic and genotypic frequencies of the SNPs were tested.

RESULTS: Although none of the SNPs tested were associated with PCV, the allelic frequencies of rs3173798 and rs3173800 were significantly different between PCV and tAMD patients. Genotype association analysis demonstrated different associations of these two SNPs between PCV and tAMD in the genotype model. Haplotype analysis revealed that the association of the major haplotype (T-T-T-T) at four selected SNPs in CD36 differed significantly between PCV and tAMD patients.

CONCLUSIONS: The CD36 region may be associated with the difference in genetic susceptibility for PCV and tAMD.

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Diet

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Lifestyle modification, nutritional and vitamins supplements for age-related macular degeneration.

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Purpose: To provide a systematic review of the published studies pertaining to the lifestyle modification, dietary, nutritional and vitamins supplements for preventing occurrence or halting deterioration of age-related macular degeneration (AMD).

Methods: The literature searches from 1990 to December 2010 with following keywords, 'age related macular degeneration', 'nutrition', 'antioxidant', 'diet' and 'vitamins supplements' using search engines Pubmed, Google Scholar, Medline and the Cochrane Library. Meta-analyses, population-based cohort studies and case-controlled trials were reviewed, whereas small cases series, case reports, commentaries, abstracts in proceedings or personal observations were excluded.

Results: Smoking and obesity are identified risk factors for AMD. High dietary intakes of omega-3 fatty acids, and macular xanthophylls lutein and zeaxanthin have been associated with a lower risk of prevalence and incidence in AMD. Vitamin B and extracts from wolfberry, Gingko biloba and berry anthocyanins were also subjects of intense research interests, but there has been no concluding scientific evidence yet. The Age-Related Eye Disease study (AREDS) is the only large-scale randomized controlled clinical trial to show beneficial effect of AREDS formulation of vitamins C, E, beta-carotene and zinc with copper in reducing the risk progression to advanced AMD in patients with intermediate AMD or with advanced AMD in one eye.

Conclusion: Quit smoking is an important advice to patients to prevent or slow the progress of AMD. There is no recommendation for routine nutritional or vitamins supplementation for primary prevention. However, patients with documented intermediate risk of AMD or advanced AMD in one eye are recommended to take AREDS-type vitamin supplements.

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