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MD Research News

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Drug treatment

Ophthalmology. 2013 Aug 2. pii: S0161-6420(13)00524-1. doi: 10.1016/j.ophtha.2013.06.020. [Epub ahead of print]

Ranibizumab versus Bevacizumab for Neovascular Age-related Macular Degeneration: Results from the GEFAL Noninferiority Randomized Trial.

Kodjikian L, Souied EH, Mimoun G, Mauget-Faÿsse M, Behar-Cohen F, Decullier E, Huot L, Aulagner G; GEFAL Study Group.

Hospices Civils de Lyon, Groupement Hospitalier Nord, Hôpital de la Croix-Rousse, Service d'ophtalmologie, Lyon, France; Université de Lyon, Lyon, France; CNRS UMR 5510 Mateis, Villeurbanne, France. Electronic address: laurent.kodjikian@chu-lyon.fr.

OBJECTIVE: To evaluate the relative efficacy and safety profile of bevacizumab versus ranibizumab intravitreal injections for the treatment of neovascular age-related macular degeneration (AMD).

DESIGN: Multicenter, prospective, noninferiority, double-masked, randomized clinical trial performed in 38 French ophthalmology centers. The noninferiority limit was 5 letters.

PARTICIPANTS: Patients aged ≥50 years were eligible if they presented with subfoveal neovascular AMD, with best-corrected visual acuity (BVCA) in the study eye of between 20/32 and 20/320 measured on the Early Treatment of Diabetic Retinopathy Study chart and a lesion area of less than 12 optic disc areas (DA).

METHODS: Patients were randomly assigned to intravitreal administration of bevacizumab (1.25 mg) or ranibizumab (0.50 mg). Hospital pharmacies were responsible for preparing, blinding, and dispensing treatments. Patients were followed for 1 year, with a loading dose of 3 monthly intravitreal injections, followed by an as-needed regimen (1 injection in case of active disease) for the remaining 9 months with monthly follow-up.

MAIN OUTCOME MEASURES: Mean change in visual acuity at 1 year.

RESULTS: Between June 2009 and November 2011, 501 patients were randomized. In the per protocol analysis, bevacizumab was noninferior to ranibizumab (bevacizumab minus ranibizumab +1.89 letters; 95% confidence interval [CI], -1.16 to +4.93, P < 0.0001). The intention-to-treat analysis was concordant. The mean number of injections was 6.8 in the bevacizumab group and 6.5 in the ranibizumab group (P = 0.39). Both drugs reduced the central subfield macular thickness, with a mean decrease of 95 μm for bevacizumab and 107 μm for ranibizumab (P = 0.27). There were no significant differences in the presence of subretinal or intraretinal fluid at final evaluation, dye leakage on angiogram, or change in choroidal

neovascular area. The proportion of patients with serious adverse events was 12.6% in the bevacizumab group and 12.1% in the ranibizumab group (P = 0.88). The proportion of patients with serious systemic or ocular adverse events was similar in both groups.

CONCLUSIONS: Bevacizumab was noninferior to ranibizumab for visual acuity at 1 year with similar safety profiles. Ranibizumab tended to have a better anatomic outcome. The results are similar to those of previous head-to-head studies.

PMID: 23916488 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2013 Aug 8. doi: 10.1136/bjophthalmol-2013-303394. [Epub ahead of print]

Different antivascular endothelial growth factor treatments and regimens and their outcomes in neovascular age-related macular degeneration: a literature review.

Lanzetta P, Mitchell P, Wolf S, Veritti D.

Department of Ophthalmology, University of Udine, Udine, Italy.

Abstract: Antivascular endothelial growth factor (anti-VEGF) therapy has revolutionised the treatment of wet age-related macular degeneration (wAMD). Recent research has focused on evaluating competing agents and alternative dosage regimens, providing evidence to help determine optimal treatment strategies. We therefore conducted a review of clinical research studies in wAMD published since 2008 that compared anti -VEGF dosing regimens and therapies; seven studies met our inclusion criteria. Data on baseline disease characteristics, disease outcomes, safety (ocular and systemic) and treatment burden (injection and visit frequencies) were extracted on patients treated with ranibizumab 0.5 mg, bevacizumab 1.25 mg or aflibercept 2.0 mg for up to 2 years. For ranibizumab and bevacizumab, visual and anatomical outcomes at 1 and 2 years were superior using scheduled monthly (or 4 weekly (q4w)) compared with as needed or scheduled quarterly dosing regimens. Treatment outcomes were generally better for both drugs when more aggressive retreatment criteria were used, which resulted in more frequent injections. Bevacizumab, however, was associated with a 30-35% elevated rate of serious systemic adverse events compared with ranibizumab, regardless of dosing interval; further study in larger patient populations will be required to determine the validity of this finding. Intravitreal aflibercept injection every 8 weeks was non-inferior to ranibizumab q4w on all visual and anatomical endpoints at week 52, had a similar safety profile and required five fewer anti-VEGF injections.

PMID: 23929309 [PubMed - as supplied by publisher]

Arq Bras Oftalmol. 2013 Jun;76(3):180-4.

Intravitreal bevacizumab combined with infliximab in the treatment of choroidal neovascularization secondary to age-related macular degeneration: case report series.

Freitas LG, Isaac DL, Tannure WT, Gabriel LA, Reis RG, Rassi AR, Freitas CA, Avila MP.

PURPOSE: To evaluate the feasibility of the combined use of bevacizumab (Avastin®) and combined with infliximab (Remicade®) in the treatment of naive choroidal neovascularization due to age-related macular degeneration eyes.

METHODS: Intravitreal injections of bevacizumab combined with infliximab in 6 neovascular age-related macular degeneration eyes. All patients underwent complete ophthalmologic examination on the initial visit and at days 1, 30, 60, 90, 120, 150 and 180 following the first injection. Optical coherence tomography and fluorescein angiography were performed during at initial visit and monthly during the 6 months follow-up period. Electroretinography was performed before and 30 days after initial injection, in order to evaluate

retinal toxicity induced by such treatment.

RESULTS: Thirty days after the first injection, 5 eyes (83%) shown decrease in macular thickness. No change was seen in electroretinogram in any eyes compared to initially performed electroretinogram. All phakic eyes developed cataract. One patient developed vitritis and was submitted to medical treatment successfully. At the end of the 6 months follow-up period, 4 patients showed significant improvement in the exudative process of choroidal neovascularization. One eye had mild persistent submacular fluid without active choroidal neovascularization, and another eye had persistent amount of intraretinal fluid due to active choroidal neovascularization.

CONCLUSION: The combined use of bevacizumab with infliximab in eyes with neovascular age-related macular degeneration was effective in reducing leakage and improving the macular thickness. However, it is not possible to assert that the results were related to synergic effects of the combination therapy. A controlled study with more cases is necessary to precisely define the complication rates; however the dosage and/or association of drugs studied in this research should not be recommended in clinical practice due to cataract as well as inflammatory reaction.

PMID: 23929080 [PubMed - in process]

Other treatment & diagnosis

Acta Biomater. 2013 Aug 2. pii: S1742-7061(13)00377-2. doi: 10.1016/j.actbio.2013.07.029. [Epub ahead of print]

Primordium of an artificial Bruch's membrane made of nanofibers for engineering of retinal pigment epithelium cell monolayers.

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Abstract: Transplanted Retinal Pigment Epithelium(RPE) cells hold promise for treatment of Age-related Macular Degeneration(AMD) and Stargardt Disease(SD), but it is conceivable that the degenerated host Bruch's membrane(BM) as a natural substrate for RPE might not optimally support transplanted cell survival with correct cellular organization. We fabricated novel ultrathin 3-dimensional(3D) nanofibrous membranes from Collagen type I and poly(lactic-co-glycolic acid) (PLGA) by an advanced clinical-grade needle-free-electrospinning process. The nanofibrillar 3D networks highly mimicked the fibrillar architecture of the native inner collagenous layer of human BM. Human RPE cells grown on our nanofibrous membranes bore striking resemblance to native human RPE. They exhibited a correctly orientated monolayer with polygonal cell shape and abundant sheet-like microvilli on their apical surfaces. RPE cells built tight junctions and expressed RPE65 protein. Flat 2-dimensional (2D) PLGA film and cover glass as controls delivered inferior RPE layers. Our nanofibrous membranes may imitate the natural BM to such extent that they allow for the engineering of in vivo-like human RPE monolayer and maintaining its biofunctional characteristics. Such ultrathin membranes may provide a promising vehicle for a functional RPE cell monolayer implantation in the subretinal space in patients with AMD or SD.

PMID: 23917149 [PubMed - as supplied by publisher]

Nat Med. 2013 Aug;19(8):998-1004. doi: 10.1038/nm.3267. Epub 2013 Aug 6.

Tumorigenicity as a clinical hurdle for pluripotent stem cell therapies.

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Abstract: Human pluripotent stem cells (PSCs) are a leading candidate for cell-based therapies because of their capacity for unlimited self renewal and pluripotent differentiation. These advances have recently culminated in the first-in-human PSC clinical trials by Geron, Advanced Cell Technology and the Kobe Center for Developmental Biology for the treatment of spinal cord injury and macular degeneration. Despite their therapeutic promise, a crucial hurdle for the clinical implementation of human PSCs is their potential to form tumors in vivo. In this Perspective, we present an overview of the mechanisms underlying the tumorigenic risk of human PSC-based therapies and discuss current advances in addressing these challenges.

PMID: 23921754 [PubMed - in process]

Proc Natl Acad Sci U S A. 2013 Aug 5. [Epub ahead of print]

Optical imaging of the chorioretinal vasculature in the living human eye.

Kim DY, Fingler J, Zawadzki RJ, Park SS, Morse LS, Schwartz DM, Fraser SE, Werner JS.

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Abstract: Detailed visualization of microvascular changes in the human retina is clinically limited by the capabilities of angiography imaging, a 2D fundus photograph that requires an intravenous injection of fluorescent dye. Whereas current angiography methods enable visualization of some retinal capillary detail, they do not adequately reveal the choriocapillaris or other microvascular features beneath the retina. We have developed a noninvasive microvascular imaging technique called phase-variance optical coherence tomography (pvOCT), which identifies vasculature three dimensionally through analysis of data acquired with OCT systems. The pvOCT imaging method is not only capable of generating capillary perfusion maps for the retina, but it can also use the 3D capabilities to segment the data in depth to isolate vasculature in different layers of the retina and choroid. This paper demonstrates some of the capabilities of pvOCT imaging of the anterior layers of choroidal vasculature of a healthy normal eye as well as of eyes with geographic atrophy (GA) secondary to age-related macular degeneration. The pvOCT data presented permit digital segmentation to produce 2D depth-resolved images of the retinal vasculature, the choriocapillaris, and the vessels in Sattler's and Haller's layers. Comparisons are presented between en face projections of pvOCT data within the superficial choroid and clinical angiography images for regions of GA. Abnormalities and vascular dropout observed within the choriocapillaris for pvOCT are compared with regional GA progression. The capability of pvOCT imaging of the microvasculature of the choriocapillaris and the anterior choroidal vasculature has the potential to become a unique tool to evaluate therapies and understand the underlying mechanisms of age-related macular degeneration progression.

PMID: 23918361 [PubMed - as supplied by publisher]

Pathogenesis

Neurosci Res. 2013 Jul 31. pii: S0168-0102(13)00182-X. doi: 10.1016/j.neures.2013.07.005. [Epub ahead of print]

Mitochondrial ferritin in neurodegenerative diseases.

Yang H, Yang M, Guan H, Liu Z, Zhao S, Takeuchi S, Yanagisawa D, Tooyama I.

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Abstract: Mitochondrial ferritin (FtMt) is a novel protein encoded by an intronless gene mapped to chromosome 5q23.1. Ferritin is ubiquitously expressed; however, FtMt expression is restricted to specific tissues such as the testis and the brain. The distribution pattern of FtMt suggests a functional role for this protein in the brain; however, data concerning the roles of FtMt in neurodegenerative diseases remain scarce. In the human cerebral cortex, FtMt expression was increased in Alzheimer's disease patients compared to control cases. Cultured neuroblastoma cells showed low-level expression of FtMt, which was increased by H2O2 treatment. FtMt overexpression showed a neuroprotective effect against H2O2-induced oxidative stress and Aβ-induced neurotoxicity in neuroblastoma cells. FtMt expression was also detected in dopaminergic neurons in the substantia nigra and was increased in patients with restless legs syndrome, while FtMt had a protective effect against cell death in a neuroblastoma cell line model of Parkinson's disease. FtMt is involved in other neurodegenerative diseases such as age-related macular degeneration (AMD), with an FtMt gene mutation identified in AMD patients, and Friedreich's ataxia, which is caused by a deficiency in frataxin. FtMt overexpression in frataxin-deficient cells increased cell resistance to H2O2 damage. These results implicate a neuroprotective role of FtMt in neurodegenerative diseases.

PMID: 23916831 [PubMed - as supplied by publisher]

Biochem Biophys Res Commun. 2013 Jul 31. pii: S0006-291X(13)01271-0. doi: 10.1016/j.bbrc.2013.07.097. [Epub ahead of print]

Epigallocatechin-gallate (EGCG) regulates autophagy in human retinal pigment epithelial cells: A potential role for reducing UVB light-induced retinal damage.

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Abstract: Autophagy is an intracellular catabolic process involved in protein and organelle degradation via the lysosomal pathway that has been linked in the pathogenesis of age-related macular degeneration (AMD). UVB irradiation-mediated degeneration of the macular retinal pigment epithelial (RPE) cells is an important hallmark of AMD, which is along with the change in RPE autophagy. Thus, pharmacological manipulation of RPE autophagy may offer an alternative therapeutic target in AMD. Here, we found that epigallocatechin-3-gallate (EGCG), a polyphenolic compound from green tea, plays a regulatory role in UVB irradiation-induced autophagy in RPE cells. UVB irradiation results in a marked increase in the amount of LC3-II protein in a dose-dependent manner. EGCG administration leads to a significant reduction in the formation of LC3-II and autophagosomes. mTOR signaling activation is required for EGCG-induced LC3-II formation, as evidenced by the fact that EGCG-induced LC3-II formation is significantly impaired by rapamycin administration. Moreover, EGCG significantly alleviates the toxic effects of UVB irradiation on RPE cells in an autophagy-dependent manner. Collectively, our study reveals a novel role of EGCG in RPE autophagy. EGCG may be exploited as a potential therapeutic reagent for the treatment of pathological conditions associated with abnormal autophagy.

PMID: 23916613 [PubMed - as supplied by publisher]

PLoS One. 2013 Jul 29;8(7):e69994. doi: 10.1371/journal.pone.0069994. Print 2013.

TNF-α Decreases VEGF Secretion in Highly Polarized RPE Cells but Increases It in Non-Polarized RPE Cells Related to Crosstalk between JNK and NF-κB Pathways.

Terasaki H, Kase S, Shirasawa M, Otsuka H, Hisatomi T, Sonoda S, Ishida S, Ishibashi T, Sakamoto T.

Department of Ophthalmology, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan.

Abstract: Asymmetrical secretion of vascular endothelial growth factor (VEGF) by retinal pigment epithelial (RPE) cells in situ is critical for maintaining the homeostasis of the retina and choroid. VEGF is also involved in the development and progression of age-related macular degeneration (AMD). We studied the effect of tumor necrosis factor-α (TNF-α) on the secretion of VEGF in polarized and non-polarized RPE cells (P-RPE cells and N-RPE cells, respectively) in culture and in situ in rats. A subretinal injection of TNF-α caused a decrease in VEGF expression and choroidal atrophy. Porcine RPE cells were seeded on Transwell™ filters, and their maturation and polarization were confirmed by the asymmetrical VEGF secretion and trans electrical resistance. Exposure to TNF-α decreased the VEGF secretion in P-RPE cells but increased it in N-RPE cells in culture. TNF-α inactivated JNK in P-RPE cells but activated it in N-RPE cells, and TNF-α activated NF-κB in P-RPE cells but not in N-RPE cells. Inhibition of NF-κB activated JNK in both types of RPE cells indicating crosstalk between JNK and NF-κB. TNF-α induced the inhibitory effects of NF-κB on JNK in P-RPE cells because NF-κB is continuously inactivated. In N-RPE cells, however, it was not evident because NF-κB was already activated. The basic activation pattern of JNK and NF-κB and their crosstalk led to opposing responses of RPE cells to TNF-α. These results suggest that VEGF secretion under inflammatory conditions depends on cellular polarization, and the TNF-α-induced VEGF down-regulation may result in choroidal atrophy in polarized physiological RPE cells. TNF-α-induced VEGF up-regulation may cause neovascularization by non-polarized or non-physiological RPE cells.

PMID: 23922887 [PubMed - in process] PMCID: PMC3726732

PLoS One. 2013 Jul 29;8(7):e69563. doi: 10.1371/journal.pone.0069563. Print 2013.

Autophagy Activation Clears ELAVL1/HuR-Mediated Accumulation of SQSTM1/p62 during Proteasomal Inhibition in Human Retinal Pigment Epithelial Cells.

Viiri J, Amadio M, Marchesi N, Hyttinen JM, Kivinen N, Sironen R, Rilla K, Akhtar S, Provenzani A, D'Agostino VG, Govoni S, Pascale A, Agostini H, Petrovski G, Salminen A, Kaarniranta K.

Department of Ophthalmology, Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland.

Abstract: Age-related macular degeneration (AMD) is the most common reason of visual impairment in the elderly in the Western countries. The degeneration of retinal pigment epithelial cells (RPE) causes secondarily adverse effects on neural retina leading to visual loss. The aging characteristics of the RPE involve lysosomal accumulation of lipofuscin and extracellular protein aggregates called "drusen". Molecular mechanisms behind protein aggregations are weakly understood. There is intriguing evidence suggesting that protein SQSTM1/p62, together with autophagy, has a role in the pathology of different degenerative diseases. It appears that SQSTM1/p62 is a connecting link between autophagy and proteasome mediated proteolysis, and expressed strongly under the exposure to various oxidative stimuli and proteasomal inhibition. ELAVL1/HuR protein is a post-transcriptional factor, which acts mainly as a positive regulator of gene expression by binding to specific mRNAs whose corresponding proteins are fundamental for key cellular functions. We here show that, under proteasomal inhibitor MG-132, ELAVL1/HuR is up-regulated at both mRNA and protein levels, and that this protein binds and post-transcriptionally regulates SQSTM1/p62 mRNA in ARPE-19 cell line. Furthermore, we observed that proteasomal inhibition caused accumulation of SQSTM1/p62 bound irreversibly to perinuclear protein aggregates. The addition of the AMPK activator AICAR was pro-survival and promoted cleansing by autophagy of the former complex, but not of the ELAVL1/HuR accumulation, indeed suggesting that SQSTM1/p62 is decreased through autophagy-mediated degradation, while ELAVL1/HuR through the proteasomal pathway. Interestingly, when compared to human controls, AMD donor samples show strong SQSTM1/p62 rather than ELAVL1/HuR accumulation in the drusen rich macular area suggesting impaired autophagy in the pathology of AMD.

PMID: 23922739 [PubMed - in process] PMCID: PMC3726683

PLoS One. 2013 Jul 26;8(7):e69552. doi: 10.1371/journal.pone.0069552. Print 2013.

Choroid sprouting assay: an ex vivo model of microvascular angiogenesis.

Shao Z, Friedlander M, Hurst CG, Cui Z, Pei DT, Evans LP, Juan AM, Tahir H, Duhamel F, Chen J, Sapieha P, Chemtob S, Joyal JS, Smith LE.

Department of Ophthalmology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, United States of America.

Abstract: Angiogenesis of the microvasculature is central to the etiology of many diseases including proliferative retinopathy, age-related macular degeneration and cancer. A mouse model of microvascular angiogenesis would be very valuable and enable access to a wide range of genetically manipulated tissues that closely approximate small blood vessel growth in vivo. Vascular endothelial cells cultured in vitro are widely used, however, isolating pure vascular murine endothelial cells is technically challenging. A microvascular mouse explant model that is robust, quantitative and can be reproduced without difficulty would overcome these limitations. Here we characterized and optimized for reproducibility an organotypic microvascular angiogenesis mouse and rat model from the choroid, a microvascular bed in the posterior of eye. The choroidal tissues from C57BL/6J and 129S6/SvEvTac mice and Sprague Dawley rats were isolated and incubated in Matrigel. Vascular sprouting was comparable between choroid samples obtained from different animals of the same genetic background. The sprouting area, normalized to controls, was highly reproducible between independent experiments. We developed a semi-automated macro in ImageJ software to allow for more efficient quantification of sprouting area. Isolated choroid explants responded to manipulation of the external environment while maintaining the local interactions of endothelial cells with neighboring cells, including pericytes and macrophages as evidenced by immunohistochemistry and fluorescence-activated cell sorting (FACS) analysis. This reproducible ex vivo angiogenesis assay can be used to evaluate angiogenic potential of pharmacologic compounds on microvessels and can take advantage of genetically manipulated mouse tissue for microvascular disease research.

PMID: 23922736 [PubMed - in process] PMCID: PMC3724908

Invest Ophthalmol Vis Sci. 2013 Aug 8. pii: iovs.12-11380v1. doi: 10.1167/iovs.12-11380. [Epub ahead of print]

The Role of Macrophage Class A Scavenger Receptors in a laser-induced Murine Choroidal Neovascularization Model.

Jawad S, Liu B, Li Z, Katamay R, Campos MM, Wei L, Sen HN, Ling D, Martinez FO, Amaral J, Chan CC, Fariss R, Gordon S, Nussenblatt RB.

Laboratory of Immunology, National Eye Institute, Bld 10, Room 10N113, Bethesda, Maryland, 20814, United States.

PURPOSE: Laser-induced choroidal neovascularization (CNV) is a widely used model to mimic many features of CNV resulting from wet age related macular degeneration (AMD). Macrophages have been implicated in the pathogenesis of AMD. Class A scavenger receptors, SR-A and MARCO, are expressed on macrophages and are associated with macrophage function. The goal of this study is to examine the role of macrophage scavenger receptors in immune cell recruitment and the formation of CNV.

METHODS: Laser photocoagulation was performed in Wild Type and knockout mice with deletion of SR-A (SR-A-/-), MARCO (MARCO-/-), or both SR-A and MARCO (DKO). Immune cell recruitment at different time points and CNV lesions at 14 days after laser treatment were evaluated through immunostaining and confocal microscopy. Microarray analysis was performed in eyes 1 day after laser injury.

RESULTS: Wild Type eyes showed higher chemokine/receptor expression compared with knockout eyes after laser injury. Scavenger receptor deficiency markedly impaired the recruitment of neutrophils and

macrophages to CNV lesions at 1 day and 3 days post laser injury, respectively. Significantly reduced CNV volumes were found in the eyes from scavenger receptor knockout mice compared with Wild Type mice.

CONCLUSIONS: The deficiency of scavenger receptors impairs the formation of CNV and immune cell recruitment. Our findings suggest a potential role for scavenger receptors in contributing to CNV formation and inflammation in AMD.

PMID: 23927892 [PubMed - as supplied by publisher]

J Biol Chem. 2013 Aug 7. [Epub ahead of print]

Exosomes from retinal astrocytes contain anti-angiogenic components that inhibit laser-induced choroidal neovascularization.

Hajrasouliha AR, Jiang G, Lu Q, Lu H, Kaplan HJ, Zhang HG, Shao H.

University of Louisville, United States.

Abstract: Exosomes released from different types of host cells have different biological effects. We report that exosomes released from retinal astroglial cells (RACs) suppress retinal vessel leakage and inhibit choroidal neovascularization (CNV) in a laser-induced CNV model, whereas exosomes released from retinal pigmental epithelium (RPE) do not. RAC exosomes inhibit the migration of macrophages and the tubule forming of mouse retinal microvascular endothelial cells (mRMVEC). Further, we analyze anti-angiogenic components in RAC exosomes using angiogenesis array kit and detect several endogenous inhibitors of angiogenesis exclusively present in RAC exosomes, such as endostatin. Moreover, blockade of matrix metalloproteinases (MMPs) in the cleavage of collagen XVIII to form endostatin using FN-439 reverses RAC exosomes-mediated retinal vessel leakage. This study demonstrates that exosomes released from retinal tissue cells have different angiogenic effects, with exosomes from RACs containing anti-angiogenic components that might protect eye from angiogenesis and maintain the functional integrity. In addition, by identifying additional components and their functions of RAC exosomes, we might improve the anti-angiogenic therapy for CNV in age-related macular degeneration (AMD) and diabetic retinopathy (DR).

PMID: 23926109 [PubMed - as supplied by publisher]

Epidemiology

PLoS One. 2013 Jun 19;8(6). doi: 10.1371/annotation/bc36f952-ec0c-45d0-bedd-15429017791e. Print 2013.

Correction: Aspirin Use and Risk of Age-Related Macular Degeneration: A Meta-Analysis.

Zhu W, Wu Y, Xu D, Li YH, Jun B, Zhang XL, Wang F, Yu J.

[This corrects the article on p. e58821 in vol. 8.].

PMID: 23922623 [PubMed - as supplied by publisher] PMCID: PMC3692953

Genetics

PLoS One. 2013 Jul 29;8(7):e70193. doi: 10.1371/journal.pone.0070193. Print 2013.

Association between CFH Y402H Polymorphism and Age Related Macular Degeneration in North

Indian Cohort.

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Abstract: The purpose of the study was to determine serum complement factor H (CFH) levels in patients of age related macular degeneration (AMD) and examine its association with CFH Y402H polymorphism. 115 AMD patients and 61 normal controls were recruited in this study. The single nucleotide polymorphism was assayed by real time PCR and serum CFH levels were measured by ELISA and standardized to total serum protein. Chi-square test was applied to polymorphism analysis while Mann Whitney U-statistic for CFH-levels. Mendelian randomization approach was used for determining causal relationship. The genotype frequency differed between the AMD patients (TT- 18.3%, TC-41.3% and CC-40.4%) and controls (TT-76.3%, TC-13.6%, and CC-10.1%) (p=0001). The frequency of alleles was also significantly different when AMD (T-39% and C-61%) was compared to controls (T-83% and C-17%) (p=0.0001). Level of serum CFH was significantly lower in AMD patients as compared to normal controls (p=0.001). Our data showed that the CFH Y402H polymorphism is a risk factor for AMD in the North Indian population. Mendelian randomization approach revealed that CFH Y402H polymorphism affects AMD risk through the modification of CFH serum levels.

PMID: 23922956 [PubMed - in process] PMCID: PMC3726372

Diet

PLoS One. 2013 Jul 29;8(7):e70948. doi: 10.1371/journal.pone.0070948. Print 2013.

The Association between Plasma 25-Hydroxyvitamin D and Subgroups in Age-Related Macular Degeneration: A Cross-Sectional Study.

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Department of Ophthalmology, Clinical Eye Research Unit, Copenhagen University Hospital, Roskilde, Denmark and University of Copenhagen, Copenhagen, Denmark.

OBJECTIVES: To evaluate potential differences in plasma 25-hydroxyvitamin in subtypes of age-related macular degeneration (AMD), and in patients in Clinical Age-Related Maculopathy Staging (CARMS) group 5 with or without subretinal fibrosis.

METHODS: This single-center cross-sectional study included 178 participants during a period of 20 months. Ninety-five patients belonged to CARMS 5; twelve belonged to CARMS 4; twenty-two belonged to CARMS 2 or 3; and 49 individuals did not have AMD (CARMS 1). Following a structured interview, a detailed bilateral retinal examination was performed and participants were allocated to their respective subgroups in accordance with the Clinical Age-Related Maculopathy Staging system. Plasma 25-hydroxyvitamin D2 and D3 were analyzed using liquid chromatography-tandem mass spectrometry. Genomic DNA was extracted from leukocytes and genotyped for single nucleotide polymorphisms (SNPs) in the vitamin D metabolism. Differences in plasma 25-hydroxyvitamin D were determined in the subgroups as well as between patients in CARMS 5 with or without subretinal fibrosis.

RESULTS: Plasma 25-hydroxyvitamin D was comparable in patients across CARMS groups 1 to 5 (p= 0.83). In CARMS 5, the presence of subretinal fibrosis was associated with significantly lower concentrations of 25-hydroxyvitamin D as compared to the absence of subretinal fibrosis (47.2 versus 75.6 nmol/L, p<0.001). Patients in CARMS 5 with subretinal fibrosis were more likely to have insufficient levels of 25-hydroxyvitamin D compared to patients without subretinal fibrosis (p=0.006). No association was found between the SNPs rs10877012, rs2228570, rs4588, or rs7041 and AMD subgroups or plasma 25-

hydroxyvitamin levels.

CONCLUSIONS: This study suggests that the presence of subretinal fibrosis in patients belonging to CARMS 5 may be associated with a poor vitamin D status. Our observations warrant further investigation into the role of vitamin D in the development of subretinal fibrosis.

PMID: 23923033 [PubMed - in process] PMCID: PMC3726594