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Drug treatment

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Long-term results of intravitreal ranibizumab for the treatment of retinal angiomatous proliferation and utility of an advanced RPE analysis performed using spectral-domain optical coherence tomography.

Inoue M, Arakawa A, Yamane S, Kadonosono K.

PURPOSE: To report the results of 3-year follow-up examinations after intravitreal ranibizumab (IVR) injection for the treatment of retinal angiomatous proliferation (RAP) and to examine the utility of an advanced retinal pigment epithelium (RPE) analysis performed using spectral-domain optical coherence tomography (SD-OCT).

METHODS: We retrospectively reviewed 17 treatment-naïve eyes in 14 patients (4 men, 10 women; age range 71-87 years; mean age 80 years) treated with IVR. All the patients received three consecutive monthly injections of 0.5 mg/0.05 mL of ranibizumab as an induction treatment. Retreatment was allowed if evidence of clinical deterioration was noted or if an SD-OCT examination performed at a 1-month follow-up showed intraretinal oedema, subretinal fluid, or recurrent pigment epithelial detachment. The primary outcome measures were best-corrected visual acuity (BCVA) and central foveal thickness (CFT) as evaluated using SD-OCT. Furthermore, we investigated the atrophic area at 36 months using advanced RPE analysis provided by SD-OCT and analysed the correlation with the BCVA.

RESULTS: The mean BCVA was well maintained from 0.57 at baseline to 0.52 at 36 months (p=0.219). The CFT decreased significantly from 317 to 223 µm at 36 months (p<0.001). The mean number of injections was 10.2. Sixteen of the 17 patients (94.1%) showed recurrence during the maintenance phase. Better visual acuity at 36 months was also associated with better visual acuity at baseline and absence of macular atrophy (MA) identified with advanced RPE analysis at 36 months (p<0.001, p=0.012, respectively).

CONCLUSIONS: The intravitreal injection of ranibizumab was effective for stabilising vision in patients with RAP, as evaluated at a 3-year follow-up examination. Advanced RPE analysis is useful for investigating atrophic areas after IVR. Visual acuity at baseline and progression of MA might be important for BCVA after IVR.

PMID: 24599418 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2014 Mar 2;8:343-6. doi: 10.2147/OPTH.S56539. eCollection 2014.

Response of serous retinal pigment epithelial detachments to intravitreal aflibercept in polypoidal choroidal vasculopathy refractory to ranibizumab.

Yamashita M, Nishi T, Hasegawa T, Ogata N.

PURPOSE: To report the effects of aflibercept on eyes with large retinal pigment epithelial detachment (PED) associted with polypoidal choroidal vasculopathy (PCV).

METHODS: We reviewed the medical records of patients with PEDs associated with PCV that were treated with aflibercept after intravitreal ranibizumab had failed.

RESULTS: Three eyes of patients aged 72, 79, and 80 years were studied. Reflective material was seen in the PED along the outer surface of the retinal pigment epithelium (RPE) by spectral-domain optical coherence tomography (SD-OCT). A complete resolution of the serous PEDs was found after two aflibercept injections; however, all eyes had a fibrovascular PED. In addition, one eye developed a retinal hemorrhage and a recurrent PED just after the third injection of aflibercept. The visual acuity in this eye decreased from 10/20 to 2/20.

CONCLUSION: The reflective material below the outer surface of the RPE in serous PED suggests the presence of neovascularization. Intravitreal aflibercept could be considered for large PEDs in eyes with PCV but should be carefully applied.

PMID: 24591809 [PubMed] PMCID: PMC3935506

Small. 2014 Mar 5. doi: 10.1002/smll.201303433. [Epub ahead of print]

Topical Delivery of Avastin to the Posterior Segment of the Eye In Vivo Using Annexin A5-associated Liposomes.

Davis BM, Normando EM, Guo L, O'Shea P, Moss SE, Somavarapu S, Cordeiro MF.

Abstract: Effective delivery to the retina is presently one of the most challenging areas in drug development in ophthalmology, due to anatomical barriers preventing entry of therapeutic substances. Intraocular injection is presently the only route of administration for large protein therapeutics, including the anti-Vascular Endothelial Growth Factors Lucentis (ranibizumab) and Avastin (bevacizumab). Anti-VEGFs have revolutionised the management of age-related macular degeneration and have increasing indications for use as sight-saving therapies in diabetes and retinal vascular disease. Considerable resources have been allocated to develop non-invasive ocular drug delivery systems. It has been suggested that the anionic phospholipid binding protein annexin A5, may have a role in drug delivery. In the present study we demonstrate, using a combination of in vitro and in vivo assays, that the presence of annexin A5 can significantly enhance uptake and transcytosis of liposomal drug carrier systems across corneal epithelial barriers. This system is employed to deliver physiologically significant concentrations of Avastin to the posterior of the rat eye (127 ng/g) and rabbit retina (18 ng/g) after topical application. Our observations provide evidence to suggest annexin A5 mediated endocytosis can enhance the delivery of associated lipidic drug delivery vehicles across biological barriers, which may have therapeutic implications.

PMID: 24596245 [PubMed - as supplied by publisher]

Expert Rev Clin Pharmacol. 2014 Mar 3. [Epub ahead of print]

Current and investigational pharmacotherapeutic approaches for modulating retinal angiogenesis.

Todorich B, Yiu G, Hahn P.

Abstract: Retinal vascular development is a carefully orchestrated developmental process during which retinal and choroidal vasculature form to provide a dual vascular supply to the neurosensory retina and retinal pigment epithelium. The most common causes of vision loss in children and adults involve at least in part perturbation of the normal vascular physiology or development. Vascular endothelial growth factor has emerged as a key molecular regulator of retinal vascular development as well as retinal and choroidal neovascularization, which underlie the pathophysiology of many retinal diseases. Over the past decade, the advent of injectable pharmacotherapeutic agents into the vitreous cavity of the eye has revolutionized our management of neovascular age-related macular degeneration and other retinal diseases and has, for the first time, offered an opportunity to improve vision rather than just slow the progression of disease processes. The transient duration of these agents, however, requires chronic treatment with repeated intraocular injections and significant treatment burden for patients and the healthcare system. Novel treatments modulating retinal angiogenesis offer the promise of improved efficacy, decreased treatment burden and improved cost-effectiveness.

PMID: 24580084 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Med Hypothesis Discov Innov Ophthalmol. 2012 Winter;1(4):72-5.

Serous pigment epithelium detachment associated with age-related macular degeneration: a possible treatment approach.

V Pasyechnikova N, A Naumenko V, R Korol A, S Zadorozhnyy O, B Kustrin T, O Nasinnyk I.

Abstract: To evaluate the effects of intravitreal triamcinolone acetonide (TA) as a monotherapy of serous Pigment Epithelial Detachment (PED) associated with AMD (Age-Related Macular Degeneration), this study has been performed. Seventeen patients (19 eyes) with serous PED associated with AMD were observed. All patients received 0.1ml (4mg) of intravitreal TA. The mean follow-up period was 18 months. Re-attachment of serous PED was observed in 37% of cases to the end of follow-up. In other cases, the height and length of serous PED significantly decreased. Visual acuity remained stable in all cases. No evidence of RPE tear or CNV development were noted. Before TA administration, intraocular pressure (IOP) was 20.18 ± 2.58 mmHg however, after intravitreal TA, IOP increased gradually and reached its maximum of all period of observation (23.25±1.85mmHg) six months after injection (P=0.031). In 7 (37%) of the cases, progression to cataract was observed after treatment. After surgery, the visual acuity in all cases increased by 0.2 to 0.5. As a conclusion, intravitreal TA decreases of both the height and length of serous PED associated with AMD after 18 months follow-up in most cases. The presented data provides support for the hypothesis regarding the possibility of monotherapy of serous PED with intravitreal TA.

PMID: 24600628 [PubMed]

Med Hypothesis Discov Innov Ophthalmol. 2012 Summer;1(2):37-41.

Is reticular macular disease a choriocapillaris perfusion problem?

A Martillo M, Marsiglia M, D Lee M, Pumariega N, Bearelly S, Smith RT.

Abstract: The etiology of reticular macular disease (RMD), a sub-phenotype of age-related macular degeneration (AMD), is controversial and has not been clarified. RMD is suspected to be a multifactorial, complex disease with genetic, environmental, and systemic factors playing an important role in its origin. Findings from combinations of different imaging modalities suggest that the pattern that characterizes this condition is associated with an alteration of the choriocapillaris blood flow. If the choroid is indeed affected in RMD, the possible linkage with inflammatory or other systemic diseases could be better supported.

PMID: 24600618 [PubMed]

Pathogenesis

Med Hypothesis Discov Innov Ophthalmol. 2012 Summer;1(2):24-32.

Melatonin and abeta, macular degeneration and alzheimers disease: same disease, different outcomes?

Vladan B, Panfoli I.

Abstract: Aging is the common denominator and the highest risk factor for macular degeneration and Alzheimers Disease (AD). Important pathological hallmarks common to both diseases are the presence of amyloid β (Aβ) in the senile plaques of the AD brain and in the drusen of age-related macular degeneration (AMD) patients, oxidative stress, and apoptotic cell death. Data suggest that a common pathogenic mechanism might exist between AMD and AD. Brain and eye depend on redox electrons from pyridinic and flavinic nucleotides to produce ATP, and reactive oxygen intermediates (ROI). Disorganization of mitochondrial structure and decline in mitochondrial oxidative phosphorylation (OXPHOS) functioning, as well as hypometabolism and alterations in mitochondrial DNA are aging features. Because ROI damage and mitochondrial dysregulation are prominent in AMD and AD and their relationship to the redox state is unclear we addressed a new hypothesis according to which the interaction of melatonin vs Aβ are intertwined to balance of the intra- and extra-mitochondrial energy production. This balance would be impaired by the ageing process and environmental/genetic factors, ultimately leading to AD and /or AMD.

PMID: 24600616 [PubMed]

J Neurosci. 2014 Mar 5;34(10):3793-806. doi: 10.1523/JNEUROSCI.3153-13.2014.

Macroglia-Microglia Interactions via TSPO Signaling Regulates Microglial Activation in the Mouse Retina.

Wang M, Wang X, Zhao L, Ma W, Rodriguez IR, Fariss RN, Wong WT.

Abstract: Chronic retinal inflammation in the form of activated microglia and macrophages are implicated in the etiology of neurodegenerative diseases of the retina, including age-related macular degeneration, diabetic retinopathy, and glaucoma. However, molecular biomarkers and targeted therapies for immune cell activation in these disorders are currently lacking. To address this, we investigated the involvement and role of translocator protein (TSPO), a biomarker of microglial and astrocyte gliosis in brain degeneration, in the context of retinal inflammation. Here, we find that TSPO is acutely and specifically upregulated in retinal microglia in separate mouse models of retinal inflammation and injury. Concomitantly, its endogenous ligand, diazepam-binding inhibitor (DBI), is upregulated in the macroglia of the mouse retina such as astrocytes and Müller cells. In addition, we discover that TSPO-mediated signaling in microglia via DBI-derived ligands negatively regulates features of microglial activation, including reactive oxygen species production, TNF-α expression and secretion, and microglial proliferation. The inducibility and effects of DBI-TSPO signaling in the retina reveal a mechanism of coordinated macroglia-microglia interactions, the function of which is to limit the magnitude of inflammatory responses after their initiation, facilitating a return to baseline quiescence. Our results indicate that TSPO is a promising molecular marker for imaging inflammatory cell activation in the retina and highlight DBI-TSPO signaling as a potential target for immodulatory therapies.

PMID: 24599476 [PubMed - in process]

PLoS One. 2014 Mar 5;9(3):e90390. doi: 10.1371/journal.pone.0090390. eCollection 2014.

Canine retina has a primate fovea-like bouquet of cone photoreceptors which is affected by inherited macular degenerations.

Beltran WA, Cideciyan AV, Guziewicz KE, Iwabe S, Swider M, Scott EM, Savina SV, Ruthel G, Stefano F, Zhang L, Zorger R, Sumaroka A, Jacobson SG, Aguirre GD.

Abstract: Retinal areas of specialization confer vertebrates with the ability to scrutinize corresponding regions of their visual field with greater resolution. A highly specialized area found in haplorhine primates (including humans) is the fovea centralis which is defined by a high density of cone photoreceptors connected individually to interneurons, and retinal ganglion cells (RGCs) that are offset to form a pit lacking retinal capillaries and inner retinal neurons at its center. In dogs, a local increase in RGC density is found in a topographically comparable retinal area defined as the area centralis. While the canine retina is devoid of a foveal pit, no detailed examination of the photoreceptors within the area centralis has been reported. Using both in vivo and ex vivo imaging, we identified a retinal region with a primate fovea-like cone photoreceptor density but without the excavation of the inner retina. Similar anatomical structure observed in rare human subjects has been named fovea-plana. In addition, dogs with mutations in two different genes, that cause macular degeneration in humans, developed earliest disease at the newly-identified canine fovea-like area. Our results challenge the dogma that within the phylogenetic tree of mammals, haplorhine primates with a fovea are the sole lineage in which the retina has a central bouquet of cones. Furthermore, a predilection for naturally-occurring retinal degenerations to alter this cone-enriched area fills the void for a clinically-relevant animal model of human macular degenerations.

PMID: 24599007 [PubMed - in process]

Biomol Ther (Seoul). 2014 Jan;22(1):1-9.

VEGF-VEGFR Signals in Health and Disease.

Shibuya M.

Abstract: Vascular endothelial growth factor (VEGF)-VEGF receptor (VEGFR) system has been shown to play central roles not only in physiological angiogenesis, but also in pathological angiogenesis in diseases such as cancer. Based on these findings, a variety of anti-angiogenic drugs, including anti-VEGF antibodies and VEGFR/multi-receptor kinase inhibitors have been developed and approved for the clinical use. While the clinical efficacy of these drugs has been clearly demonstrated in cancer patients, they have not been shown to be effective in curing cancer, suggesting that further improvement in their design is necessary. Abnormal expression of an endogenous VEGF-inhibitor sFlt-1 has been shown to be involved in a variety of diseases, such as preeclampsia and aged macular degeneration. In addition, various factors modulating angiogenic processes have been recently isolated. Given this complexity then, extensive studies on the interrelationship between VEGF signals and other angiogenesis-regulatory systems will be important for developing future strategies to suppress diseases with an angiogenic component.

PMID: 24596615 [PubMed - as supplied by publisher]

PLoS One. 2014 Feb 26;9(2):e89548. doi: 10.1371/journal.pone.0089548. eCollection 2014.

RAGE Regulates Immune Cell Infiltration and Angiogenesis in Choroidal Neovascularization.

Chen M, Glenn JV, Dasari S, McVicar C, Ward M, Colhoun L, Quinn M, Bierhaus A, Xu H, Stitt AW.

PURPOSE: RAGE regulates pro-inflammatory responses in diverse cells and tissues. This study has investigated if RAGE plays a role in immune cell mobilization and choroidal neovascular pathology that is associated with the neovascular form of age-related macular degeneration (nvAMD).

METHODS: RAGE null (RAGE-/-) mice and age-matched wild type (WT) control mice underwent laser photocoagulation to generate choroidal neovascularization (CNV) lesions which were then analyzed for morphology, S100B immunoreactivity and inflammatory cell infiltration. The chemotactic ability of bone

marrow derived macrophages (BMDMs) towards S100B was investigated.

RESULTS: RAGE expression was significantly increased in the retina during CNV of WT mice ($p<0.001$). RAGE-/- mice exhibited significantly reduced CNV lesion size when compared to WT controls ($p<0.05$). S100B mRNA was upregulated in the lasered WT retina but not RAGE-/- retina and S100B immunoreactivity was present within CNV lesions although levels were less when RAGE-/- mice were compared to WT controls. Activated microglia in lesions were considerably less abundant in RAGE-/- mice when compared to WT counterparts ($p<0.001$). A dose dependent chemotactic migration was observed in BMDMs from WT mice ($p<0.05$-0.01) but this was not apparent in cells isolated from RAGE-/- mice.

CONCLUSIONS: RAGE-S100B interactions appear to play an important role in CNV lesion formation by regulating pro-inflammatory and angiogenic responses. This study highlights the role of RAGE in inflammation-mediated outer retinal pathology.

PMID: 24586862 [PubMed - in process] PMCID: PMC3935881

PLoS One. 2014 Feb 26;9(2):e88203. doi: 10.1371/journal.pone.0088203. eCollection 2014.

Temsirolimus Inhibits Proliferation and Migration in Retinal Pigment Epithelial and Endothelial Cells via mTOR Inhibition and Decreases VEGF and PDGF Expression.

Liegl R, Koenig S, Siedlecki J, Haritoglou C, Kampik A, Kernt M.

Abstract: Due to their high prevalence, retinal vascular diseases including age related macular degeneration (AMD), retinal vein occlusions (RVO), diabetic retinopathy (DR) and diabetic macular edema have been major therapeutic targets over the last years. The pathogenesis of these diseases is complex and yet not fully understood. However, increased proliferation, migration and angiogenesis are characteristic cellular features in almost every retinal vascular disease. The introduction of vascular endothelial growth factor (VEGF) binding intravitreal treatment strategies has led to great advances in the therapy of these diseases. While the predominant part of affected patients benefits from the specific binding of VEGF by administering an anti-VEGF antibody into the vitreous cavity, a small number of non-responders exist and alternative or additional therapeutic strategies should therefore be evaluated. The mammalian target of rapamycin (mTOR) is a central signaling pathway that eventually triggers up-regulation of cellular proliferation, migration and survival and has been identified to play a key role in angiogenesis. In the present study we were able to show that both retinal pigment epithelial (RPE) cells as wells as human umbilical vein endothelial cells (HUVEC) are inhibited in proliferating and migrating after treatment with temsirolimus in non-toxic concentrations. Previous studies suggest that the production of VEGF, platelet derived growth factor (PDGF) and other important cytokines is not only triggered by hypoxia but also by mTOR itself. Our results indicate that temsirolimus decreases VEGF and PDGF expression on RNA and protein levels significantly. We therefore believe that the mTOR inhibitor temsirolimus might be a promising drug in the future and it seems worthwhile to evaluate complementary therapeutic effects with anti-VEGF drugs for patients not profiting from mono anti-VEGF therapy alone.

PMID: 24586308 [PubMed - in process] PMCID: PMC3935828

PLoS One. 2014 Feb 19;9(2):e88201. doi: 10.1371/journal.pone.0088201. eCollection 2014.

T cells and macrophages responding to oxidative damage cooperate in pathogenesis of a mouse model of age-related macular degeneration.

Cruz-Guilloty F, Saeed AM, Duffort S, Cano M, Ebrahimi KB, Ballmick A, Tan Y, Wang H, Laird JM, Salomon RG, Handa JT, Perez VL.

Abstract: Age-related macular degeneration (AMD) is a major disease affecting central vision, but the

pathogenic mechanisms are not fully understood. Using a mouse model, we examined the relationship of two factors implicated in AMD development: oxidative stress and the immune system. Carboxyethylpyrrole (CEP) is a lipid peroxidation product associated with AMD in humans and AMD-like pathology in mice. Previously, we demonstrated that CEP immunization leads to retinal infiltration of pro-inflammatory M1 macrophages before overt retinal degeneration. Here, we provide direct and indirect mechanisms for the effect of CEP on macrophages, and show for the first time that antigen-specific T cells play a leading role in AMD pathogenesis. In vitro, CEP directly induced M1 macrophage polarization and production of M1-related factors by retinal pigment epithelial (RPE) cells. In vivo, CEP eye injections in mice induced acute pro-inflammatory gene expression in the retina and human AMD eyes showed distinctively diffuse CEP immunolabeling within RPE cells. Importantly, interferon-gamma (IFN-γ) and interleukin-17 (IL-17)-producing CEP-specific T cells were identified ex vivo after CEP immunization and promoted M1 polarization in co-culture experiments. Finally, T cell immunosuppressive therapy inhibited CEP-mediated pathology. These data indicate that T cells and M1 macrophages activated by oxidative damage cooperate in AMD pathogenesis.

PMID: 24586307 [PubMed - in process] PMCID: PMC3929609

PLoS One. 2014 Feb 21;9(2):e87751. doi: 10.1371/journal.pone.0087751. eCollection 2014.

Degeneration modulates retinal response to transient exogenous oxidative injury.

Lederman M, Hagbi-Levi S, Grunin M, Obolensky A, Berenshtein E, Banin E, Chevion M, Chowers I.

PURPOSE: Oxidative injury is involved in retinal and macular degeneration. We aim to assess if retinal degeneration associated with genetic defect modulates the retinal threshold for encountering additional oxidative challenges.

METHODS: Retinal oxidative injury was induced in degenerating retinas (rd10) and in control mice (WT) by intravitreal injections of paraquat (PQ). Retinal function and structure was evaluated by electroretinogram (ERG) and histology, respectively. Oxidative injury was assessed by immunohistochemistry for 4-Hydroxy-2-nonenal (HNE), and by Thiobarbituric Acid Reactive Substances (TBARS) and protein carbonyl content (PCC) assays. Anti-oxidant mechanism was assessed by quantitative real time PCR (QPCR) for mRNA of antioxidant genes and genes related to iron metabolism, and by catalase activity assay.

RESULTS: Three days following PQ injections (1 µl of 0.25, 0.75, and 2 mM) the average ERG amplitudes decreased more in the WT mice compared with the rd10 mice. For example, following 2 mM PQ injection, ERG amplitudes reduced 1.84-fold more in WT compared with rd10 mice ($p=0.02$). Injection of 4 mM PQ resulted in retinal destruction. Altered retina morphology associated with PQ was substantially more severe in WT eyes compared with rd10 eyes. Oxidative injury according to HNE staining and TBARS assay increased 1.3-fold and 2.1-fold more, respectively, in WT compared with rd10 mice. At baseline, prior to PQ injection, mRNA levels of antioxidant genes (Superoxide Dismutase1, Glutathione Peroxidase1, Catalase) and of Transferrin measured by quantitative PCR were 2.1-7.8-fold higher in rd10 compared with WT mice ($p<0.01$ each), and catalase activity was 1.7-fold higher in rd10 ($p=0.0006$).

CONCLUSIONS: This data suggests that degenerating rd10 retinas encounter a relatively lower degree of damage in response to oxidative injury compared with normal retinas. Constitutive up-regulation of the oxidative defense mechanism in degenerating retinas may confer such relative protection from oxidative injury.

PMID: 24586289 [PubMed - in process] PMCID: PMC3931611

Biol Pharm Bull. 2014;37(3):424-30.

Protective Effect of SUN N8075, a Free Radical Scavenger, against Excessive Light-Induced Retinal Damage in Mice.

Ojino K, Shimazawa M, Ohno Y, Otsuka T, Tsuruma K, Hara H.

Abstract: Although dry age-related macular degeneration (AMD) is one of the major causes of blindness, no effective therapies are developed. In this study, we investigated the effects of SUN N8075, a radical scavenger with neuroprotective properties, against light-induced retinal damage used as the model of dry AMD in mice. After dark adaption for 24 h, we exposed the mice at 8000 lx for 3 h. We evaluated the retinal damage by recording the electroretinagram (ERG) and measuring the thickness of outer nuclear layer (ONL) at 5 d after the light exposure. Retinal apoptotic cells were also detected by terminal deoxynucleotidyl transeferase mediated deoxyuridine triphosphate (dUTP) nick end labeling (TUNEL) staining, and the expression of 8-hydroxy-2-deoxyguanosine (8-OHdG) as an index for oxidative stress at 48 h after exposure to light. In ERG measurement, the intraperitoneal administration of SUN N8075 at 30 mg/kg improved the retinal dysfunction induced by the excess light exposure. In the histological evaluation, SUN N8075 inhibited the reduction of ONL thickness. In addition, SUN N8075 decreased in both numbers of TUNEL- and 8-OHdG-positive cells in ONL. These findings suggest that the systemic administration of SUN N8075 has protective effects on excess light-induced photoreceptor degeneration, via inhibition of oxidative stress.

PMID: 24583861 [PubMed - in process]

Epidemiology

J Intern Med. 2014 Mar 1. doi: 10.1111/joim.12227. [Epub ahead of print]

Is age-related macular degeneration a manifestation of systemic disease? New prospects for early intervention and treatment.

Cheung GC, Tien Yin W.

Abstract: Age-related macular degeneration (AMD) is a common vision-threatening condition affecting the elderly. AMD shares common risk factors and processes, including vascular and inflammatory pathways, with many systemic disorders. Associations have been reported between AMD and hypertension, cardiovascular disease, cerebrovascular disease, dyslipidaemia, chronic kidney disease and neurodegenerative disorders. An increasing amount of evidence suggests that individuals with AMD are also at risk of systemic diseases such as stroke. In this review we summarize the latest evidence to support the notion that AMD is an ocular manifestation of systemic disease processes, and discuss the potential systemic side effects of ocular AMD therapy of which general physicians should be aware. Recent genetic discoveries and understanding of the pathogenic pathways in AMD in relation to systemic disorders are also highlighted.

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Med Hypothesis Discov Innov Ophthalmol. 2013 Fall;2(3):59-68.

Aspirin and Age Related Macular Degeneration; the Possible Relationship.

Wu Y, Zhu W, Li YH, Yu J.

Abstract: Age-related macular degeneration (AMD) is becoming the leading cause of blindness in developed countries. The exact etiology and pathophysiology of AMD is still unclear. A number of risk

factors of AMD have been recognized, such as cigarette smoking, a family history of AMD and being Caucasian. On the other hand, aspirin is a widespread medication, which is thought to be associated with the prevalence or the survival of myocardial infarction and cancers. However, the evidence from the epidemiological studies has been contradictory and no persuasive conclusions have been made. Several problems, such as the parameters of aspirin use, the inclusion and exclusion of the participants and the required long-term follow-up, made it hard to conclude a definite relationship between aspirin use and AMD. Aspirin, as an anti-inflammatory agent, could prevent the inflammation and decrease the inflammatory damage, and might act as a deterrent for the progression of AMD. However, aspirin is an anticoagulant which might increase the risk of ocular hemorrhage in AMD patients. Decades ago, the use of aspirin was reported associated with decreased rates of CNV among AMD patients nevertheless recently, the association between aspirin use and increased risk of neovascular AMD was identified. Therefore, these current results should be challenged and acknowledged by well-designed, large-scale and long term follow-up studies. A consultation might be needed when aspirin is used in the neovascular AMD patients.

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Br J Ophthalmol. 2014 Mar 3. doi: 10.1136/bjophthalmol-2013-304068. [Epub ahead of print]

Prevalence and causes of vision loss in North Africa and the Middle East: 1990-2010.

Khairallah M, Kahloun R, Flaxman SR, Jonas JB, Keeffe J, Leasher J, Naidoo K, Pesudovs K, Price H, White RA, Wong TY, Resnikoff S, Taylor HR, Bourne RR; on behalf of the Vision Loss Expert Group.

BACKGROUND: To describe the prevalence and causes of visual impairment and blindness in North Africa and the Middle East (NAME) in 1990 and 2010.

METHODS: Based on a systematic review of medical literature, we examined prevalence and causes of moderate and severe vision impairment (MSVI; presenting visual acuity <6/18, ≥3/60) and blindness (presenting visual acuity <3/60).

RESULTS: In NAME, the age-standardised prevalence of blindness decreased from 2.1% to 1.1% and MSVI from 7.1% to 4.5%. In 2010, 3.119 million people were blind, and 13.700 million had MSVI. Women were generally more often affected than men. Main causes of blindness were cataract, uncorrected refractive error, macular degeneration and glaucoma. Main causes of MSVI were cataract and uncorrected refractive errors. Proportions of blindness and MSVI from trachoma significantly decreased.

CONCLUSIONS: Although the absolute numbers of people with blindness and MSVI increased from 1990 to 2010, the overall age-standardised prevalence of blindness and MSVI among all ages and among those aged 50 years and older decreased significantly ($p<0.05$). Cataract and uncorrected refractive error were the major causes of blindness and MSVI.

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Genetics

Med Hypothesis Discov Innov Ophthalmol. 2013 Fall;2(3):74-82.

Instability in X chromosome inactivation patterns in AMD: a new risk factor?

Vladan B, Biljana SP, Mandusic V, Zorana M, Zivkovic L.

Abstract: Years ago, it was thought that a genetic component was the fundamental cause of a number retinopathy diseases including age related macular degeneration (AMD). Since then, information has emerged about novel genes that contribute to various forms of AMD and other retinopathies that have been

eluding researchers for years. In the genetic sense, only the APOE 2 and 4 genes have been found to be a risk factor for sporadic AMD. But, a recent Genome wide association study (GWAS) revealed that an alteration of five SNIPs on the X chromosome in a gene named DIAPH2 may be a susceptibility gene for AMD. Furthermore, the gene DIAPH2 showed to have a polygenic pleiotropy for premature ovarian failure (POF) and AMD in a cohort of women. POF is highly associated with X chromosome skewing, an epigenetic alteration of the inactivation process of the X chromosome. These findings suggest a hypothesis that an epigenetic alteration on the inactivation centres of the X chromosome (or skewing) relates not only to aging, but might be a novel property that affects women with AMD more often than men.

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Graefes Arch Clin Exp Ophthalmol. 2014 Mar 5. [Epub ahead of print]

Genetic and clinical factors associated with reticular pseudodrusen in exudative age-related macular degeneration.

Yoneyama S, Sakurada Y, Mabuchi F, Imasawa M, Sugiyama A, Kubota T, Iijima H.

BACKGROUND: Reticular pseudodrusen (RPD) is considered to be a distinct entity from soft drusen and a risk factor for age-related macular degeneration (AMD). In the present study, we investigate the genetic and clinical factors associated with reticular pseudodrusen (RPD) in patients with exudative AMD, including polypoidal choroidal vasculopathy (PCV), typical neovascular AMD, and retinal angiomatous proliferation (RAP).

METHODS: The presence or absence of RPD was studied among 408 patients with exudative AMD in at least one eye, and the clinical characteristics of those with RPD were investigated as well as genetic polymorphisms of ARMS2 A69S (rs10490924) and CFH I62V (rs800292). Subfoveal choroidal thickness was also evaluated in a limited number of subjects using the EDI mode of spectral-domain optical coherence tomography.

RESULTS: The prevalence of RPD was significantly higher in RAP eyes than in typical neovascular AMD or in PCV eyes (38.2 % of 26 eyes, 13.6 % of 132 eyes and 0 % of 250 eyes respectively, $P < 0.0001$). RPD was significantly more prevalent in the elderly ($P < 0.0001$) and female ($P < 0.0001$) subjects. The subfoveal choroidal thickness was thinner in eyes with RPD than in those without (129.7 ± 61.7 μm vs 42.6 ± 84.9 μm, $P < 0.0001$). The frequency of risk variants of ARMS2 A69S was significantly higher in eyes with RPD than in those without RPD (85.7 % vs 63.8 %, $P = 0.0009$), although the frequency of CFH I62V was not significantly different between those with and without RPD. Logistic regression analysis revealed that age (odds ratio [OR]:1.10; 95 % confidence interval [CI]: 1.04-1.18; $p = 0.002$), female gender (OR:4.26; 95%CI: 1.72-10.4; $p = 0.002$), T-allele at ARMS2 A69S (OR: 3.23; 95%CI: 1.36-7.68; $p = 0.008$) and RAP (OR: 4.25; 95%CI:1.49-12.1; $p = 0.007$) were risk factors for RPD.

CONCLUSIONS: Among eyes with exudative AMD, RPD is more common in eyes with RAP having a thin choroid at the fovea, especially in old, female patients with the risk variant of ARMS2 A69S.

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The Relationship between BCMO1 Gene Variants and Macular Pigment Optical Density in Persons with and without Age-Related Macular Degeneration.

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BACKGROUND: Recent evidence indicates that gene variants related to carotenoid metabolism play a role

in the uptake of macular pigments lutein (L) and zeaxanthin (Z). Moreover, these pigments are proposed to reduce the risk for advanced age-related macular degeneration (AMD). This study provides the initial examination of the relationship between the gene variants related to carotenoid metabolism, macular pigment optical density (MPOD) and their combined expression in healthy humans and patients with AMD.

PARTICIPANTS AND METHODS: Forty-four participants were enrolled from a general population and a private practice including 20 healthy participants and 24 patients with advanced (neovascular) AMD. Participants were genotyped for the three single nucleotide polymorphisms (SNPs) upstream from BCMO1, rs11645428, rs6420424 and rs6564851 that have been shown to either up or down regulate beta-carotene conversion efficiency in the plasma. MPOD was determined by heterochromatic flicker photometry.

RESULTS: Healthy participants with the rs11645428 GG genotype, rs6420424 AA genotype and rs6564851 GG genotype all had on average significantly lower MPOD compared to those with the other genotypes ($p<0.01$ for all three comparisons). When combining BCMO1 genotypes reported to have "high" (rs11645428 AA/rs6420424 GG/rs6564851 TT) and "low" (rs11645428 GG/rs6420424 AA/rs6564851 GG) beta-carotene conversion efficiency, we demonstrate clear differences in MPOD values ($p<0.01$). In patients with AMD there were no significant differences in MPOD for any of the three BCMO1 gene variants.

CONCLUSION: In healthy participants MPOD levels can be related to high and low beta-carotene conversion BCMO1 genotypes. Such relationships were not found in patients with advanced neovascular AMD, indicative of additional processes influencing carotenoid uptake, possibly related to other AMD susceptibility genes. Our findings indicate that specific BCMO1 SNPs should be determined when assessing the effects of carotenoid supplementation on macular pigment and that their expression may be influenced by retinal disease.

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Inherited mitochondrial DNA variants can affect complement, inflammation and apoptosis pathways: insights into mitochondrial-nuclear interactions.

Cristina Kenney M, Chwa M, Atilano SR, Falatoonzadeh P, Ramirez C, Malik D, Tarek M, Cáceres-Del-Carpio J, Nesburn AB, Boyer DS, Kuppermann BD, Vawter M, Michal Jazwinski S, Miceli M, Wallace DC, Udar N.

Abstract: Age-related macular degeneration (AMD) is the leading cause of vision loss in developed countries. While linked to genetic polymorphisms in the complement pathway, there are many individuals with high risk alleles that do not develop AMD, suggesting that other 'modifiers' may be involved. Mitochondrial (mt) haplogroups, defined by accumulations of specific mtDNA single nucleotide polymorphisms (SNPs) which represent population origins, may be one such modifier. J haplogroup has been associated with high risk for AMD while the H haplogroup is protective. It has been difficult to assign biological consequences for haplogroups so we created human ARPE-19 cybrids (cytoplasmic hybrids), which have identical nuclei but mitochondria of either J or H haplogroups, to investigate their effects upon bioenergetics and molecular pathways. J cybrids have altered bioenergetic profiles compared with H cybrids. Q-PCR analyses show significantly lower expression levels for seven respiratory complex genes encoded by mtDNA. J and H cybrids have significantly altered expression of eight nuclear genes of the alternative complement, inflammation and apoptosis pathways. Sequencing of the entire mtDNA was carried out for all the cybrids to identify haplogroup and non-haplogroup defining SNPs. mtDNA can mediate cellular bioenergetics and expression levels of nuclear genes related to complement, inflammation and apoptosis. Sequencing data suggest that observed effects are not due to rare mtDNA variants but rather the combination of SNPs representing the J versus H haplogroups. These findings represent a paradigm shift in our concepts of mt-nuclear interactions.

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Diet & lifestyle

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Relation of Smoking, Drinking, and Physical Activity to Changes in Vision over a 20-Year Period: The Beaver Dam Eye Study.

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OBJECTIVE: To describe the relationships of lifestyle characteristics to changes in vision and incidence of visual impairment (VI) over a 20-year period in the Beaver Dam Eye Study (BDES).

DESIGN: Longitudinal, population-based cohort study.

PARTICIPANTS: A cohort of 4926 persons aged 43 to 86 years participated in the baseline examinations in 1988-1990, and 3721, 2962, 2375, and 1913 persons participated in follow-up examinations in 1993-1995, 1998-2000, 2003-2005, and 2008-2010, respectively.

METHODS: Best-corrected visual acuity (BCVA) measured by a modified Early Treatment Diabetic Retinopathy Study protocol.

MAIN OUTCOME MEASURE: Change in number of letters read correctly and incidence of VI based on BCVA in the better eye assessed at each examination over a 20-year period.

RESULTS: The 20-year cumulative incidence of VI was 5.4%. There was a mean loss of 1.6 letters between examinations, with a 20-year loss of 6.6 letters. While adjusting for age, income, and age-related macular degeneration (AMD) severity, being a current or past smoker was related to a greater change in the numbers of letters lost. Persons who had not consumed alcoholic beverages over the past year and sedentary persons had higher odds of incident VI than persons who drank occasionally or who were physically active. For example, in women with early AMD and annual household income less than $10 000, the estimated 20-year cumulative incidence of VI in those who drank occasionally and were physically active was 5.9% compared with 25.8% in women who had not consumed alcoholic beverages over the past year and were sedentary.

CONCLUSIONS: Three modifiable behaviors-smoking, drinking alcohol, and physical activity-were associated with changes in vision. Further evidence that changes in these behaviors will result in less loss of vision is needed because of the expected increase in the burden of VI due to the aging of the population.

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Beneficial effect of antioxidants in retinopathies: a new hypothesis.

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Abstract: The retina is the most oxygen consuming tissue of the body. Rod and cone photoreceptors efficiently carry out visual cascades, which are energetically costly processes. Data has recently been published that suggests that the metabolic support to phototransduction in the rod outer segment (OS) may originate directly in the OS, which is able to conduct aerobic metabolism. This oxygen-handling activity of the rod OS, which was never suspected before, appears to be a primary cause of the generation of reactive oxygen species directly inside the OS. Oxidative stress has been hypothesised to contribute to most of the neurodegenerative retinal pathologies, such as diabetic retinopathy, age-related macular degeneration, retinitis pigmentosa and photoreceptor cell death after retinal detachment. Many natural antioxidant compounds are routinely used in experimental or human therapies for preventing or delaying photoreceptor

degeneration in those pathologies. Here it is proposed that the ultimate reason for the beneficial actions of antioxidants in preventing or retarding the effect on the retinal degenerative pathologies can be found in their action on reactive oxygen species generated by the ectopic mitochondrial electron transport chain (ETC) coupled to FoF1-ATP synthase in rod OS disks. In fact, if not adequately coupled, the ETC generates reactive oxygen species that, in turn, can act on the polyunsaturated fatty acids which the rod OS is rich in. If correct, the mechanism put forward here would provide a potential for the molecular basis of therapies with antioxidants for retinal degenerative diseases.

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