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## Drug treatment

**Br J Ophthalmol. 2011 Jul 6. [Epub ahead of print]**

**Tachyphylaxis during treatment of exudative age-related macular degeneration with ranibizumab.**

Eghøj MS, Sørensen TL.

Copenhagen University Hospital Roskilde, Roskilde, Denmark.

Aim: To determine whether tachyphylaxis occurs during treatment with ranibizumab (Lucentis, Genentech, Inc., South San Francisco, California, USA) for exudative age-related macular degeneration (AMD). Design Retrospective review of cases.

Participants: The treatment results of 1076 eyes (976 patients) treated with ranibizumab for exudative AMD was evaluated to identify patients with a potential tachyphylactic response. The participants had to have a minimum of 12 months follow-up.

Methods: Tachyphylaxis was defined as a lack of response to the drug at the time of reactivation of choroidal neovascularisation (CNV) in patients who had responded to the initial treatment. The authors considered it a lack of response to ranibizumab if a decrease in vision and an increase in central retinal thickness (CRT) were observed despite repeated injections. Hence a stabilisation in vision and/or stabilisation in CRT during treatment were not considered tachyphylaxis, and other unfavourable responses such as a tear in the retinal pigment epithelium and therefore a decrease in vision during treatment were also not considered as tachyphylaxis. Every patient in this cohort who has had an injection-free interval after primary inactivation of CNV and who has received retreatment at a later stage was identified. In this population, those cases that did not respond to retreatment (tachyphylaxis) were identified and characterised.

Main outcome measures: Number of patients who developed tachyphylaxis after treatment with ranibizumab.

Results 20 patients: (2%) developed tachyphylaxis during their treatment.

Conclusion: Tachyphylaxis can occur during the treatment of exudative AMD with ranibizumab. The precise mechanism for the development of tachyphylaxis is unclear. Both local and systemic factors might be involved.

PMID: 21733918 [PubMed - as supplied by publisher]

**Graefes Arch Clin Exp Ophthalmol. 2011 Jul 2. [Epub ahead of print]**

**Characteristics of eyes with secondary loss of visual acuity receiving variable dosing ranibizumab for neovascular age-related macular degeneration.**

Mariani A, Deli A, Ambresin A, Mantel I.

Ophthalmology Department, University of Lausanne, Jules-Gonin Eye Hospital, 15 Av. de France, Case Postale 133, 1000, Lausanne 7, Switzerland.

PURPOSE: The aim of this work is to investigate the characteristics of eyes failing to maintain visual acuity (VA) receiving variable dosing ranibizumab for neovascular age-related macular degeneration (nAMD) after three initial loading doses.

METHODS: A consecutive series of patients with nAMD, who, after three loading doses of intravitreal ranibizumab (0.5 mg each), were re-treated for fluid seen on optical coherence tomography. After exclusion of eyes with previous treatment, follow-up less than 12 months, or missed visits, 99 patients were included in the analysis. The influence of baseline characteristics, initial VA response, and central retinal thickness (CRT) fluctuations on the VA stability from month 3 to month 24 were analyzed using subgroups and multiple regression analyses.

RESULTS: Mean follow-up duration was 21.3 months (range 12-40 months, 32 patients followed-up for =24 months). Secondary loss of VA (loss of five letters or more) after month 3 was seen in 30 patients (mean VA improvement from baseline +5.8 letters at month 3, mean loss from baseline -5.3 letters at month 12 and -9.7 at final visit up to month 24), while 69 patients maintained vision (mean gain +8.9 letters at month 3, +10.4 letters at month 12, and +12.8 letters at final visit up to month 24). Secondary loss of VA was associated with the presence of pigment epithelial detachment (PED) at baseline (p 0.01), but not with baseline fibrosis/atrophy/hemorrhage, CRT fluctuations, or initial VA response. Chart analysis revealed additional individual explanations for the secondary loss of VA, including retinal pigment epithelial tears, progressive fibrosis, and atrophy.

CONCLUSIONS: Tissue damage due to degeneration of PED, retinal pigment epithelial tears, progressive fibrosis, progressive atrophy, or massive hemorrhage, appears to be relevant in causing secondary loss of VA despite vascular endothelial growth factor suppression. PED at baseline may represent a risk factor.

PMID: 21725716 [PubMed - as supplied by publisher]

**Nippon Ganka Gakkai Zasshi. 2011 Jun;115(6):523-8.**

**[Survey of triamcinolone-related non-infectious endophthalmitis].**

[Article in Japanese]

Sakamoto T, Ishibashi T, Ogura Y, Shiraga F, Takeuchi S, Yamashita H; Japanese Retina and Vitreous Society Triamcinolone Survey Group.

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PURPOSE: To survey non-infectious endophthalmitis related to triamcinolone acetonide (TA) for ocular diseases in Japan.

SUBJECTS AND METHODS: A questionnaire was sent to the 24 committee members of the Japanese Retina and Vitreous Society requesting information regarding non-infectious endophthalmitis related to intravitreous TA administered from January through December 2009. The survey specifically covered the use of TA in intravitreal injections and intraoperatively during vitrectomy procedures.

RESULTS: All 24 members responded to the survey involving intraviteal TA use in 562 eyes; 325 eyes for diabetic macular edema, 118 eyes for retinal vein occlusion, 91 eyes for uveitis, 11 eyes for age-related macular degeneration and 17 eyes had adjunctive use in retinal photocoagulation. Intraoperative use for visualizing vitreous was done in 6973 eyes. Noninfectious endophthalmitis occurred in 9 eyes (1.6%) after intravitreous TA and 7 eyes (0.1%) after intraoperative TA. The most frequent symptom was blurred vision with no pain or mild conjunctival injection. Sudden severe anterior chamber and vitreous inflammation occurred beginning on the day following surgery, but it disappeared spontaneously without complications.

CONCLUSIONS: It was found that non-infectious endophthalmitis occurred after intravitreous TA. Although the visual prognosis is good, this complication should be recognized by retina specialists.

PMID: 21735756 [PubMed - in process]

**Chang Gung Med J. 2011 May-Jun;34(3):320-5.**

**Retinal pigment epithelial tear after intravitreous triamcinolone acetonide injection for fibrovascular pigment epithelial detachment.**

Wu PC, Chen YJ, Kuo HK.

Department of Ophthalmology, Chang Gung Memorial Hospital - Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan.

Abstract

A 78-year-old woman was diagnosed with fibrovascular pigment epithelial detachment (PED) associated with age-related macular degeneration (AMD) affecting both eyes. Due to decreased vision in her left eye (20/2000) and disease progression, the patient received 4 mg of triamcinolone acetonide (TA) by intravitreal injection into her left eye. There were no immediate post-injection complications in the left eye. However, one week later, a retinal pigment epithelial (RPE) tear, temporal-inferior to the fovea in the left eye, was noted and confirmed by fundus photography, fluorescein angiography and optical coherence tomography. In contrast, there no similar RPE tear occurred in her right eye after treated several times by intravitreous bevacizumab injection. Not only anti-vascular endothelium growth factor agents, but also intravitreal TA when used to treat AMD with PED, would seem to induce a RPE tear in the absence of previous or concurrent adjuvant therapy. Further investigations are required to confirm the mechanism by which the RPE tear occurs.

PMID: 21733363 [PubMed - in process]

**PLoS One. 2011;6(6):e21411. Epub 2011 Jun 22.**

**Blockade of VEGFR1 and 2 Suppresses Pathological Angiogenesis and Vascular Leakage in the Eye.**

Huang H, Shen J, Vinores SA.

Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States of America.

OBJECTIVE: VEGFR1 and 2 signaling have both been increasingly shown to mediate complications of ischemic retinopathies, including retinopathy of prematurity (ROP), age-related macular degeneration (AMD), and diabetic retinopathy (DR). This study evaluates the effects of blocking VEGFR1 and 2 on pathological angiogenesis and vascular leakage in ischemic retinopathy in a model of ROP and in choroidal neovascularization (CNV) in a model of AMD.

MATERIALS AND METHODS: Neutralizing antibodies specific for mouse VEGFR1 (MF1) and VEGFR2 (DC101) were administrated systemically. CNV was induced by laser photocoagulation and assessed 14d after laser treatment. Retinal NV was generated in oxygen-induced ischemic retinopathy (OIR) and assessed at p17. NV quantification was determined by measuring NV tufts and vascular leakage was quantified by measuring [(3)H]-mannitol leakage from blood vessels into the retina. Gene expression was measured by real-time quantitative (Q)PCR.

RESULTS: VEGFR1 and VEGFR2 expressions were up-regulated during CNV pathogenesis. Both MF1 and DC101 significantly suppressed CNV at 50 mg/kg: DC101 suppressed CNV by 73±5% (p<0.0001) and MF1 by 64±6% (p?=?0.0002) in a dosage-dependent manner. The combination of MF1 and DC101 enhanced the inhibitory efficacy and resulted in an accumulation of retinal microglia at the CNV lesion. Similarly, both MF1 and DC101 significantly suppressed retinal NV in OIR at 50 mg/kg: DC101 suppressed retinal NV by 54±8% (p?=?0.013) and MF1 by 50±7% (p<0.0002). MF1 was even more effective at inhibiting ischemia-induced BRB breakdown than DC101: the retina/lung leakage ratio for MF1 was reduced by 73±24%, p?=?0.001 and for DC101 by 12±4%, p?=?0.003. The retina/renal leakage ratio for MF1 was reduced by 52±28%, p?=?0.009 and for DC101 by 13±4%, p?=?0.001.

CONCLUSION: Our study provides further evidence that both VEGFR1 and 2 mediate pathological angiogenesis and vascular leakage in these models of ocular disease and suggests that antagonist antibodies to these receptor tyrosine kinases (RTKs) are potential therapeutic agents.

PMID: 21731737 [PubMed - in process]

**Acta Ophthalmol. 2011 Jul 5. doi: 10.1111/j.1755-3768.2011.02184.x. [Epub ahead of print]**

**Panretinal photocoagulation (PRP) versus PRP plus intravitreal ranibizumab for high-risk proliferative diabetic retinopathy.**

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Department of Ophthalmology, School of Medicine of Ribeirão Preto, Ribeirão Preto, SP, Brazil Departments of Ophthalmology and Public Health Sciences, Penn State College of Medicine, Hershey, Pennsylvania, USA.

Purpose: To evaluate the effects of panretinal photocoagulation (PRP) compared with PRP plus intravitreal injection of 0.5 mg of ranibizumab (IVR) in patients with high-risk proliferative diabetic retinopathy (PDR).

Methods: Prospective study included patients with high-risk PDR and no prior laser treatment randomly assigned to receive PRP (PRP group) or PRP plus IVR (PRPplus group). PRP was administered in two sessions (weeks 0 and 2), and IVR was administered at the end of the first laser session in the PRPplus group. Standardized ophthalmic evaluations including best-corrected visual acuity (BCVA) measured according to the methods used in the Early Treatment Diabetic Retinopathy Study (BCVA), fluorescein angiography to measure area of fluorescein leakage (FLA) and optical coherence tomography (OCT) for the assessment of central subfield macular thickness (CSMT), were performed at baseline and at weeks 16 (±2), 32 (±2) and 48 (±2).

Results: Twenty-nine of 40 patients (n = 29 eyes) completed the 48-week study follow-up period. At baseline, mean ± SE FLA (mm(2) ) was 9.0 ± 1.3 and 11.7 ± 1.3 (p = 0.1502); BCVA (logMAR) was 0.31 ± 0.05 and 0.27 ± 0.06 (p = 0.6645); and CSMT (μm) was 216.3 ± 10.7 and 249.4 ± 36.1 (p = 0.3925), in the PRP and PRPplus groups, respectively. There was a significant (p < 0.05) FLA reduction at all study visits in both groups, with the reduction observed in the PRPplus group significantly larger than that in the PRP group at week 48 (PRP = 2.9 ± 1.3 mm(2) ; PRPplus = 5.8 ± 1.3 mm(2) ; p = 0.0291). Best-corrected visual acuity worsening was observed at 16, 32 and 48 weeks after treatment in the PRP group (p < 0.05), while no significant BCVA changes were observed in the PRPplus group. A significant CSMT increase was observed in the PRP group at all study visits, while a significant decrease in CSMT was observed in the

PRPplus group at week 16, and no significant difference in CSMT from baseline was observed at weeks 32 and 48.

Conclusions: Intravitreal ranibizumab after PRP was associated with a larger reduction in FLA at week 48 compared with PRP alone in eyes with high-risk PDR, and the adjunctive use of IVR appears to protect against the modest visual acuity loss and macular swelling observed in eyes treated with PRP alone.

PMID: 21726427 [PubMed - as supplied by publisher]

**Ir Med J. 2011 May;104(5):146-9.**

**Intravitreal anti-VEGF therapy for neovascular age-related macular degeneration and the risk of stroke.**

Cleary CA, Sharaznayan D, Hickey-Dwyer M.

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Abstract

The purpose of this study was to compare the vascular event rate in AMD patients treated with an intravitreal VEGF inhibitor with a historical control group treated with photodynamic therapy. We reviewed medical records of 83 patients treated with intravitreal anti-VEGF for AMD between 2005-2007, and 60 patients treated with PDT between 2001-2004. Mean follow-up in the anti-VEGF group was 40 months versus 95 months in the PDT group. Mean age (76 +/- 9 years, versus 74 +/- 10 years, p=n.s.) and cardiovascular risk factor profile were similar. Vascular event rates in each group were 2.6 per 100 patient years versus 2.3 per 100 patient years, (p = n.s). Age over 80 years was associated with an increased risk of a vascular event (odds ratio = 1.113, p<0.05). Despite the high prevalence of risk factors in AMD patients, the incidence of vascular events was low and associated with older age rather than therapy received.

PMID: 21736091 [PubMed - in process]

## Other treatment & diagnosis

**Eye (Lond). 2011 Jul 8. doi: 10.1038/eye.2011.162. [Epub ahead of print]**

**Spectral domain optical coherence tomography macular cube scans and retinal pigment epithelium/drusen maps may fail to display subretinal drusenoid deposits (reticular pseudodrusen) in eyes with non-neovascular age-related macular degeneration.**

Switzer DW, Engelbert M, Freund KB.

1] LuEsther T. Mertz Retinal Research Foundation, Manhattan Eye, Ear, and Throat Hospital, New York, NY, USA [2] Vitreous Retina Macula Consultants of New York, New York, NY, USA [3] Department of Ophthalmology, New York University School of Medicine, New York, NY, USA.

PMID: 21738232 [PubMed - as supplied by publisher]

**Med Image Anal. 2011 Jun 22. [Epub ahead of print]**

**Automated macular pathology diagnosis in retinal OCT images using multi-scale spatial pyramid and local binary patterns in texture and shape encoding.**

Liu YY, Chen M, Ishikawa H, Wollstein G, Schuman JS, Rehg JM.

School of Interactive Computing, College of Computing, Georgia Institute of Technology, Atlanta, GA, United States.

Abstract

We address a novel problem domain in the analysis of optical coherence tomography (OCT) images: the diagnosis of multiple macular pathologies in retinal OCT images. The goal is to identify the presence of normal macula and each of three types of macular pathologies, namely, macular edema, macular hole, and age-related macular degeneration, in the OCT slice centered at the fovea. We use a machine learning approach based on global image descriptors formed from a multi-scale spatial pyramid. Our local features are dimension-reduced local binary pattern histograms, which are capable of encoding texture and shape information in retinal OCT images and their edge maps, respectively. Our representation operates at multiple spatial scales and granularities, leading to robust performance. We use 2-class support vector machine classifiers to identify the presence of normal macula and each of the three pathologies. To further discriminate sub-types within a pathology, we also build a classifier to differentiate full-thickness holes from pseudo-holes within the macular hole category. We conduct extensive experiments on a large dataset of 326 OCT scans from 136 subjects. The results show that the proposed method is very effective (all AUC>0.93).

PMID: 21737338 [PubMed - as supplied by publisher]

**Ophthalmology. 2011 Jul 1. [Epub ahead of print]**

**Natural History of Drusen Morphology in Age-Related Macular Degeneration Using Spectral Domain Optical Coherence Tomography.**

Yehoshua Z, Wang F, Rosenfeld PJ, Penha FM, Feuer WJ, Gregori G.

Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida.

PURPOSE: To characterize the natural history of drusen using spectral-domain optical coherence tomography (SD-OCT) imaging of eyes from patients with nonexudative age-related macular degeneration (AMD).

DESIGN: Prospective, longitudinal, natural history study.

PARTICIPANTS: We included 143 eyes of 100 patients with at least 6 months of follow-up.

METHODS: Patients with drusen secondary to nonexudative AMD were scanned using the Cirrus SD-OCT instrument. Eyes were imaged using the 200×200 A-scan raster pattern contained within a 6×6 mm area. Custom software was used to quantify volumetric changes in drusen over a period of =6 months and for as long as 24 months. Drusen volume and drusen area were measured within circular regions centered at the fovea having diameters of 3 and 5 mm. The measurements were analyzed using a suitable scale transformation. For drusen volume, a cube root transformation strategy was used.

MAIN OUTCOME MEASURES: Change in drusen volume and area over time.

RESULTS: We analyzed 143 eyes of 100 patients with 69 eyes followed for 6 months, 106 eyes followed for 12 months, 48 eyes followed for 18 months, and 48 eyes followed for 24 months. The 3 mm circle baseline drusen volume ranged from 0.0009 to 0.7479 mm(3) or 0.10 to 0.91 mm using the cube root scale. On average, drusen volume and drusen area increased over time with the magnitude of the increase dependent on the length of follow-up (P = 0.001, 3 mm circle). In the eyes with a decrease in drusen volume, the magnitude of this decrease was dependent on the baseline drusen volume (P = 0.001, 3 mm circle) and independent of the follow-up interval. After 12 months, drusen volume increased in 48% of eyes, remained stable in 40%, and decreased in 12%.

CONCLUSIONS: Imaging with SD-OCT revealed a dynamic, undulating growth pattern for drusen with a tendency for drusen to increase in volume and area over time. An appreciation of the quantitative changes in drusen volume over time using SD-OCT imaging provides a novel strategy for following normal disease progression and for identifying novel clinical trial end points to be used when investigating therapies for the treatment of nonexudative AMD.

PMID: 21724264 [PubMed - as supplied by publisher]

**Ophthalmology. 2011 Jun 30. [Epub ahead of print]**

**Comparative Effectiveness and Cost-Effectiveness of the Implantable Miniature Telescope.**

Brown GC, Brown MM, Lieske HB, Lieske PA, Brown KS, Lane SS.

Center for Value-Based Medicine, Flourtown, Pennsylvania; Eye Research Institute, Philadelphia, Pennsylvania; The Retina Service, Wills Eye Institute, Jefferson Medical College, Philadelphia, Pennsylvania.

OBJECTIVE: To assess the preference-based comparative effectiveness (human value gain) and the cost-utility (cost-effectiveness) of a telescope prosthesis (implantable miniature telescope) for the treatment of end-stage, age-related macular degeneration (AMD).

DESIGN: A value-based medicine, second-eye model, cost-utility analysis was performed to quantify the comparative effectiveness and cost-effectiveness of therapy with the telescope prosthesis.

PARTICIPANTS: Published, evidence-based data from the IMT002 Study Group clinical trial. Ophthalmic utilities were obtained from a validated cohort of >1000 patients with ocular diseases.

METHODS: Comparative effectiveness data were converted from visual acuity to utility (value-based) format. The incremental costs (Medicare) of therapy versus no therapy were integrated with the value gain conferred by the telescope prosthesis to assess its average cost-utility. The incremental value gains and incremental costs of therapy referent to (1) a fellow eye cohort and (2) a fellow eye cohort of those who underwent intra-study cataract surgery were integrated in incremental cost-utility analyses. All value outcomes and costs were discounted at a 3% annual rate, as per the Panel on Cost-Effectiveness in Health and Medicine.

MAIN OUTCOME MEASURES: Comparative effectiveness was quantified using the (1) quality-adjusted life-year (QALY) gain and (2) percent human value gain (improvement in quality of life). The QALY gain was integrated with incremental costs into the cost-utility ratio ($/QALY, or US dollars expended per QALY gained).

RESULTS: The mean, discounted QALY gain associated with use of the telescope prosthesis over 12 years was 0.7577. When the QALY loss of 0.0004 attributable to the adverse events was factored into the model, the final QALY gain was 0.7573. This resulted in a 12.5% quality of life gain for the average patient during the 12 years of the model. The average cost-utility versus no therapy for use of the telescope prosthesis was $14389/QALY. The incremental cost-utility referent to control fellow eyes was $14063/QALY, whereas the incremental cost-utility referent to fellow eyes that underwent intra-study cataract surgery was $11805/QALY.

CONCLUSIONS: Therapy with the telescope prosthesis considerably improves quality of life and at the same time is cost-effective by conventional standards.

PMID: 21723614 [PubMed - as supplied by publisher]

Vestn Oftalmol. 2011 Mar-Apr;127(2):36-9.

[Visual fixation features after treatment of exudative age macular degeneration].

[Article in Russian]

[No authors listed]

Abstract

Changes of visual fixation in patients with choroidal neovascularitation (CNV) associated with age macular degeneration (AMD) after bevacizumab are studied. 45 patients (45 eyes) with active CNV treated with intravitreal bevacizumab were enrolled into the study. Visual fixation was studied before and 3-6 months after treatment using original method that included fundus foto and fluorescein angiography. Fixation relative to fovea and lesion was evaluated. Foveal fixation beyond lesion was found in 9%, foveal fixation within lesion --in 47%, extrafoveal fixation beyond lesion--in 18%, extrafoveal fixation within lesion--in 26% of patients. Changes of fixation localization after treatment was found in 24% patients. Examination of visual fixation may be useful for prognosis of anti-VEGF treatment efficacy in patients with CNV.

PMID: 21721271 [PubMed - in process]

## Pathogenesis

**Invest Ophthalmol Vis Sci. 2011 Jul 1. [Epub ahead of print]**

**The Role of Bcl-xL in Mouse RPE Cell Survival.**

Medearis S, Han IC, Huang JK, Yang P, Jaffe GJ.

Ophthalmology, Duke University Eye Center, Durham, NC;

Purpose: RPE cell survival plays a critical role in normal physiology and in retinal diseases, such as age-related macular degeneration (AMD) and proliferative vitreoretinopathy (PVR). We have previously demonstrated that Bcl-x(L) is an important cell survival protein in human RPE (hRPE) cells. Herein, we determined the role of Bcl-x(L) as a survival protein in mouse RPE (mRPE) cells.

Methods: Survival factor gene expression and Bcl-x(L) protein distribution were determined using qRT-PCR and immunohistochemistry, respectively. Cultured mRPE cells were transfected with two modified 2'-O-methoxyethoxy antisense oligonucleotides (ASOs): Bcl-x(L) mismatched control and Bcl-x(L)-specific. Bcl-x(L) protein levels were analyzed using Western blot. To determine the effects of survival factor regulation in mRPE cells, cultured cells were treated for 24 hours with mouse TNF-a, human IL-1ß, and human TNF-a.

Results: Bcl-x(L) was the most highly expressed survival factor in both mouse eyecup and cultured mRPE cells, while Bax was the most highly expressed anti-survival factor. Bcl-x(L) was expressed in the RPE layer, and the distribution among the retinal layers was similar to that observed in human eyecups. IL-1ß and TNF-a had minimal effect on Bcl-x(L) and Bax expression and strongly up-regulated Traf-1. Transfection with Bcl-x(L)-specific ASO resulted in markedly diminished Bcl-x(L) gene expression, Bcl-x(L) protein levels, and cell number.

Conclusions: Bcl-x(L) is the most highly expressed survival gene in mRPE cells and is essential for mRPE cell survival. Our data suggest that mouse tissue is an appropriate model for investigations of RPE survival factor genes.

PMID: 21724914 [PubMed - as supplied by publisher]

# Genetics

**Curr Opin Ophthalmol. 2011 Jul 1. [Epub ahead of print]**

**Mitochondrial disorders and the eye.**

Schrier SA, Falk MJ.

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PURPOSE OF REVIEW: Mitochondrial disease is a heterogeneous group of energy metabolism disorders that present across all ages with a wide range of ocular or multisystemic manifestations. This review focuses on recent progress made toward understanding the various ophthalmologic manifestations of primary mitochondrial diseases and discusses the implications of mitochondrial dysfunction, placing particular emphasis on recent investigations into the pathogenesis and emerging therapies for mitochondrial-based ophthalmologic disorders.

RECENT FINDINGS: Novel pathogenic mitochondrial DNA mutations continue to be detected in diverse ethnic populations for primary mitochondrial ophthalmologic disorders that commonly affect the optic nerve, retina, and extraocular muscles. Promising antioxidant and gene therapy approaches are being actively investigated to treat these ophthalmologic manifestations, as in Leber's hereditary optic neuropathy. Mitochondrial dysfunction is also increasingly implicated in common ophthalmologic disorders of aging, including diabetic retinopathy, age-related macular degeneration, and glaucoma. Several proteins recently recognized to play a role in the mitochondrial oxidative stress response within retinal cells, such as prohibitin and MMP2, may serve as novel biomarkers and therapeutic targets for common ophthalmologic disorders. Therapies that inhibit mitochondrial function and induce apoptosis within tumor cells, such as EDL-155 and curcumin, may offer novel therapeutic agents for ocular neoplasms such as retinoblastoma and uveal melanoma.

SUMMARY: Primary mitochondrial genetic disease manifestations can involve almost all aspects of the eye. Mitochondrial dysfunction is increasingly recognized as playing a causative role in the common ophthalmologic disorders in aging. This understanding has unleashed a range of emerging therapeutic approaches for mitochondrial-based ophthalmologic disorders directed at optimizing mitochondrial function.

PMID: 21730846 [PubMed - as supplied by publisher]

**Exp Eye Res. 2011 Jun 26. [Epub ahead of print]**

**Elevated membrane attack complex in human choroid with high risk complement factor H genotypes.**

Mullins RF, Dewald AD, Streb LM, Wang K, Kuehn MH, Stone EM.

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Abstract

Data from human genetics, histopathology, and animal models reveal a major role for the complement system in the development of age-related macular degeneration (AMD). Genetic variations in the complement factor H (CFH) gene are associated with an elevated risk of AMD. In this study we sought to determine whether eyes from donors with a high-risk genotype (homozygosity for the histidine allele at codon 402) exhibit altered levels of membrane attack complex (MAC) in the choroid, compared to eyes with a low risk genotype (homozygosity for tyrosine). Proteins were extracted from the RPE/choroid of 18 donors (10 low risk and 8 high risk) and levels of MAC were assessed using an ELISA assay. Eyes from donors homozy-

gous for the histidine allele showed 69% higher levels of MAC than those homozygous for the tyrosine allele ($p < 0.05$), independent of whether the eyes showed signs of early AMD. Our results provide evidence that high-risk CFH genotypes may affect AMD risk by increased deposition of MAC around the aging choriocapillaris.

PMID: 21729696 [PubMed - as supplied by publisher]

**PLoS One. 2011;6(6):e20707. Epub 2011 Jun 27.**

**Regulation of retinoschisin secretion in weri-rb1 cells by the f-actin and microtubule cytoskeleton.**

Kitamura E, Gribanova YE, Farber DB.

Jules Stein Eye Institute and Department of Ophthalmology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, United States of America.

Abstract

Retinoschisin is encoded by the gene responsible for X-linked retinoschisis (XLRS), an early onset macular degeneration that results in a splitting of the inner layers of the retina and severe loss in vision. Retinoschisin is predominantly expressed and secreted from photoreceptor cells as a homo-oligomer protein; it then associates with the surface of retinal cells and maintains the retina cellular architecture. Many missense mutations in the XLRS1 gene are known to cause intracellular retention of retinoschisin, indicating that the secretion process of the protein is a critical step for its normal function in the retina. However, the molecular mechanisms underlying retinoschisin's secretion remain to be fully elucidated. In this study, we investigated the role of the F-actin cytoskeleton in the secretion of retinoschisin by treating Weri-Rb1 cells, which are known to secrete retinoschisin, with cytochalasin D, jasplakinolide, Y-27632, and dibutyryl cGMP. Our results show that cytochalasin D and jasplakinolide inhibit retinoschisin secretion, whereas Y-27632 and dibutyryl cGMP enhance secretion causing F-actin alterations. We also demonstrate that high concentrations of taxol, which hyperpolymerizes microtubules, inhibit retinoschisin secretion. Our data suggest that retinoschisin secretion is regulated by the F-actin cytoskeleton, that cGMP or inhibition of ROCK alters F-actin structure enhancing the secretion, and that the microtubule cytoskeleton is also involved in this process.

PMID: 21738583 [PubMed - in process]