

Issue 128

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

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Drug treatment

Graefes Arch Clin Exp Ophthalmol. 2013 Apr 19. [Epub ahead of print]

Ranibizumab for exudative AMD in a clinical setting: differences between 2007 and 2010.

Cohen SY, Dubois L, Ayrault S, Dourmad P, Delahaye-Mazza C, Fajnkuchen F, Nghiem-Buffer S, Quentel G, Tadayoni R.

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BACKGROUND/PURPOSE: Visual results of ranibizumab given pro re nata in clinical settings depend greatly from the achievement of the monthly follow-up. In 2007, a previous study performed in our tertiary care showed a mean visual gain of only + 0.7 ETDRS chart letters, probably because of insufficient number of follow-up visits and injections. We report a second retrospective study of patients whose eyes were treated in the same setting, and whose first injection was performed after April 1 2010. The aim was to check if the changes in the management of AMD patients between 2010 and 2007 achieved better visual results.

METHOD: One hundred and twenty-two patients (125 eyes) with exudative age-related macular degeneration (AMD) were included. Age, gender, side, type of CNV, VA measured on an ETDRS chart at baseline and at 52 ± 6 weeks, the number of IVT performed, and follow-up visits were recorded. The series was compared to our former series of the year 2007. Results are expressed as means $\pm$ standard deviation. Mann-Whitney's non-parametric test was used to compare the statistical distribution of the parameters measured. Fisher's exact test was used for 2×2 categorical variables, and the chi-square test for others.

RESULTS: In the 2010 series, the mean visual gain was $+6.0 \pm 11.0$ l (-35 to + 34). During this period, the eyes had 5.0 ± 1.8 IVT and 7.8 ± 1.4 follow-up visits. No correlation was found between the change in VA and gender, type of CNV, age, or the numbers of IVT and visits. There was a reverse correlation between baseline VA and VA changes ($r = -0.413$, $p < 0.0001$): i.e., the higher the VA at presentation, the smaller the gain. Comparison between 2010 and 2007 showed that in 2010, patients were older (82.2 ± 7.0 vs 78.3 ± 7.0 y, $p < 0.0001$), had a better baseline VA (60.6 ± 12.7 vs 56.1 ± 14.6 l, $p = 0.0191$) and, despite the reverse correlation between change in VA and VA at presentation, visual results were better: $+6.0 \pm 11.0$ vs $+0.7 \pm 11.99$ l, $p = 0.0003$. In 2010, eyes received more injections: 5.0 ± 1.8 vs 3.8 ± 1.4 in 2007, $p < 0.0001$. However, the series did not differ for the number of visits, gender, side or type of CNV.

CONCLUSIONS: In 2010, monotherapy with ranibizumab for exudative AMD achieved better visual results than in 2007 in our clinical setting, despite the treatment of older patients with better baseline VA. This is probably due to the greater number of IVT performed. Alternate strategies, such as "inject and extend" or

maintenance therapy, may also account for the better visual results.

PMID: 23604514 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2013;7:757-63. doi: 10.2147/OPTH.S42189. Epub 2013 Apr 19.

Two-year outcomes of pro re nata ranibizumab monotherapy for exudative age-related macular degeneration in Japanese patients.

Yamamoto A, Okada AA, Sugitani A, Kunita D, Rii T, Yokota R.

Department of Ophthalmology, Kyorin University School of Medicine, Tokyo, Japan.

PURPOSE: To describe outcomes of intravitreal ranibizumab using a pro re nata regimen for treatment-naïve exudative age-related macular degeneration (AMD), in Japanese patients over the first 2 years.

METHODS: Clinical records were retrospectively reviewed of 48 eyes of 48 patients with treatment-naïve exudative AMD who underwent intravitreal ranibizumab therapy. After three monthly injections (induction), patients were examined monthly, and subsequent injections were performed as needed (pro re nata) for any residual activity, by fundus biomicroscopy and imaging studies, regardless of severity.

RESULTS: Twenty-nine (60%) of the patients were men, and 19 (40%) were women; the mean age was 76.1 years. Of the 48 eyes evaluated, 17 (35%) had findings consistent with polypoidal choroidal vasculopathy, and five (10%) with retinal angiomatous proliferation. A mean of 6.0 ranibizumab injections were given in the first year, 3.5 in the second year, and 9.5 over the 2-year period. The best-corrected visual acuity (logarithm of minimum angle of resolution) improved significantly, from 0.35 at baseline to 0.21 at 12 months ($P < 0.01$), and remained stable at 0.21 at 24 months ($P < 0.01$). The mean central macular thickness decreased significantly, from 355.4 μm at baseline to 237.9 μm at 12 months ($P < 0.01$) and 247.7 μm at 24 months ($P < 0.01$).

CONCLUSION: Improved visual acuity and decreased central macular thickness were observed and maintained over a 2-year period, in a Japanese population receiving 3 monthly induction injections followed by a pro re nata regimen of ranibizumab for exudative AMD.

PMID: 23620657 [PubMed - in process]

Retina. 2013 Apr 22. [Epub ahead of print]

FACTORS PREDICTIVE OF OUTCOMES 1 YEAR AFTER 3 MONTHLY RANIBIZUMAB INJECTIONS AND AS-NEEDED REINJECTIONS FOR POLYPOIDAL CHOROIDAL VASCULOPATHY IN JAPANESE PATIENTS.

Hikichi T, Higuchi M, Matsushita T, Kosaka S, Matsushita R, Takami K, Ohtsuka H.

Ohtsuka Eye Hospital, Sapporo, Japan.

PURPOSE: To determine baseline factors predictive of outcomes 1 year after 3 monthly intravitreal ranibizumab injections followed by as-needed injections for polypoidal choroidal vasculopathy.

METHODS: A nonrandomized prospective 1-year trial collected data from 144 Japanese patients (144 eyes) with symptomatic polypoidal choroidal vasculopathy who received one 0.5-mg intravitreal ranibizumab injection monthly for 3 months followed by as-needed retreatments. Statistical analysis evaluated baseline independent factors predictive of better visual acuity and the need for fewer injections 1 year after the first injection.

RESULTS: After the initial 3 monthly injections, a mean $\pm$ standard deviation of 1.2 ± 1.1 as-needed

injections was administered. The mean visual acuity improved significantly ($P < 0.01$) from 20/80 to 20/50. Better visual acuity and no history of photodynamic therapy or clusters of grape-like polypoidal lesions were significant independent baseline factors predictive of better visual acuity 1 year after the first injection. No factors were significantly associated with a need for fewer ranibizumab reinjections during follow-up.

CONCLUSION: The baseline clinical characteristics predicted favorable visual acuity outcomes. These findings might be useful to explaining the prognosis of ranibizumab treatment to the patients with polypoidal choroidal vasculopathy.

PMID: 23612049 [PubMed - as supplied by publisher]

Retina. 2013 Apr 23. [Epub ahead of print]

INTRAVITREAL BEVACIZUMAB IN THE MANAGEMENT OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: Effect of Baseline Visual Acuity.

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PURPOSE: To study prospectively the safety and efficacy of intravitreal bevacizumab for eyes with neovascular age-related macular degeneration with baseline visual acuity better than 70 letters (Snellen equivalent better than 20/40).

METHODS: Patients with treatment-naïve neovascular age-related macular degeneration were categorized prospectively into three groups according to baseline visual acuity: Group 1 (better than 70 letters), Group 2 (70 to 61 letters), and Group 3 (60 to 51 letters). Best-corrected visual acuity and central retinal thickness using optical coherence tomography were measured at baseline and at each follow-up visit. Intravitreal bevacizumab was administered according to an as-needed optical coherence tomography-guided regimen. Main outcome measure was mean best-corrected visual acuity for each group at 12 months.

RESULTS: Each group included 30 patients (30 eyes). Improvement in central retinal thickness was similar among the 3 groups ($P = 0.964$). Mean letter gain in visual acuity at 12 months was +0.4, +3.8, and +4.2 for Groups 1, 2, and 3, respectively ($P = 0.42$). Mean best-corrected visual acuity at 12 months was 78.4 letters for Group 1, 70.0 letters for Group 2, and 61.1 letters for Group 3 ($P < 0.001$). All eyes in Group 1 (100%) avoided losing 15 letters of best-corrected visual acuity versus 83.3% in Group 2 and 80.0% in Group 3. This difference was significant only between Group 1 and Group 3 ($P = 0.02$).

CONCLUSION: Intravitreal bevacizumab for eyes with neovascular age-related macular degeneration and baseline visual acuity better than 70 letters was safe and able to maintain this vision over 12 months.

PMID: 23615342 [PubMed - as supplied by publisher]

Retina. 2013 Apr 19. [Epub ahead of print]

BIMANUAL ASSISTED EYELID RETRACTION TECHNIQUE FOR INTRAVITREAL INJECTIONS.

Fineman MS, Hsu J, Spirn MJ, Kaiser RS.

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PURPOSE: To describe an alternative technique for avoiding contact with the lids and eyelashes without the use of a metal lid speculum along with the results in clinical practice.

METHODS: Retrospective review of the medical records of all patients undergoing intravitreal injections of bevacizumab and ranibizumab with lid retraction achieved by bimanual assisted eyelid retraction between November 2010 and December 2011.

RESULTS: A total of 10,164 consecutive intravitreal injections were performed, of which 3,834 were bevacizumab and 6,330 were ranibizumab. In this cohort of patients, 3 suspected cases of endophthalmitis developed (2 culture-negative), corresponding to a rate of 0.03%.

CONCLUSION: The technique of bimanual assisted eyelid retraction for intravitreal injection has a low rate of infection similar to the reported rates using a metal lid speculum.

PMID: 23609121 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Invest Ophthalmol Vis Sci. 2013 Apr 25. pii: iovs.13-11804v1. doi: 10.1167/iov.13-11804. [Epub ahead of print]

Methods and Reproducibility of Grading Optimized Digital Color Fundus Photographs in the Age-Related Eye Disease Study 2 (AREDS2)(AREDS2 Report Number 2).

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PURPOSE: To establish continuity with the grading procedures and outcomes from the historical data of the Age-Related Eye Disease Study (AREDS), color photographic imaging and evaluation procedures for the assessment of age-related macular degeneration (AMD) were modified for digital imaging in the AREDS2. The reproducibility of the grading of index AMD lesion components and for the AREDS Severity Scale was tested at the AREDS2 Reading Center.

METHODS: Digital color stereoscopic fundus photographs from 4203 AREDS2 subjects collected at baseline and annual follow-up visits were optimized for tonal balance and graded according to a standard protocol slightly modified from AREDS. The reproducibility of digital grading of AREDS2 images was assessed by reproducibility exercises; temporal drift (regrading a subset of baseline annually, n=88) and contemporaneous masked regrading (ongoing, monthly regrade on 5% of submissions, n=1335 eyes).

RESULTS: In AREDS2, 91% and 96% of images received replicate grades within 2 steps of the baseline value on the AREDS Severity Scale for temporal drift and contemporaneous assessment, respectively (weighted Kappa of 0.73 and 0.76). Historical data for temporal drift in replicate gradings on the AREDS film-based images was 88% within 2 steps (weighted Kappa = 0.88). There was no difference in AREDS2-AREDS concordance for temporal drift (exact P = 0.57).

CONCLUSIONS: Digital color grading has nearly the same reproducibility as historical film grading. There is substantial agreement for testing the predictive utility of the AREDS Severity Scale in AREDS2 as a clinical trial outcome.

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Invest Ophthalmol Vis Sci. 2013 Apr 25. pii: iovs.12-10465v1. doi: 10.1167/iov.12-10465. [Epub ahead of print]

Static and Flicker Perimetry in Age-Related Macular Degeneration.

Luu CD, Dimitrov PN, Wu Z, Ayton LN, Makeyeva G, Aung KZ, Varsamidis M, Robman L, Vingrys AJ, Guymer RH.

Centre for Eye Research Australia, University of Melbourne, Royal Victorian Eye and Ear Hospital, Macular Research Unit, Level 1, 32 Gisborne Street, East Melbourne, VIC, 3002, Australia.

Purpose: The relationship between clinical severity of age-related macular degeneration (AMD) and macular function has not been well established. In this study, we investigated the correlation between clinical severity and functional deficits as detected by static and flicker perimetry.

Methods: This cross-sectional study consisted of 279 AMD subjects and 24 control participants. AMD subjects were allocated into 1 of 10 AMD severity groups depending on the status of both the designated study eye and the fellow eye, as assessed by colour fundus photographs. Visual acuity and both static and flicker perimetry were tested on one eye during the same session. The geometric means, standard deviations and percentage of abnormal eyes of both static and flicker sensitivity of each AMD severity group were determined and compared.

Results: The pattern of change in sensitivity and percentage of abnormal eyes for static perimetry across all AMD severity groups were similar to flicker perimetry. Eyes with drusen $\geq 125\mu\text{m}$ [$p(\text{static}) = 0.018$; $p(\text{flicker}) = 0.024$], drusenoid epithelial detachment [$p(\text{static} \& \text{flicker}) 0.001$] and non central GA [$p(\text{static} \& \text{flicker}) 0.001$] had significant reductions in both static and flicker sensitivities compared to normal eyes. Both static [β -coefficient, 95%CI: -1.59, -4.78 to 1.60] and flicker [β -coefficient, 95%CI: -1.29, -4.66 to 2.08] sensitivities declined at a similar rate in eyes that showed clinical signs of progression.

Conclusions: Static and flicker perimetry were similarly affected across the spectrum of AMD severity and both methods appeared to be valid techniques for assessing retinal sensitivity in AMD once drusen $>125\mu\text{m}$ are present but before the development of late AMD.

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J Neural Eng. 2013 Apr 23;10(3):036013. [Epub ahead of print]

Spatially restricted electrical activation of retinal ganglion cells in the rabbit retina by hexapolar electrode return configuration.

Habib AG, Cameron MA, Suaning GJ, Lovell NH, Morley JW.

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Objective: Visual prostheses currently in development aim to restore some form of vision to patients suffering from diseases such as age-related macular degeneration and retinitis pigmentosa. Most rely on electrically stimulating inner retinal cells via electrodes implanted on or near the retina, resulting in percepts of light termed 'phosphenes'. Activation of spatially distinct populations of cells in the retina is key for pattern vision to be produced. To achieve this, the electrical stimulation must be localized, activating cells only in the direct vicinity of the stimulating electrode(s). With this goal in mind, a hexagonal return (hexapolar) configuration has been proposed as an alternative to the traditional monopolar or bipolar return configurations for electrically stimulating the retina. This study investigated the efficacy of the hexapolar configuration in localizing the activation of retinal ganglion cells (RGCs), compared to a monopolar configuration.

Approach: Patch-clamp electrophysiology was used to measure the activation thresholds of RGCs in whole-mount rabbit retina to monopolar and hexapolar electrical stimulation, applied subretinally.

Main results: Hexapolar activation thresholds for RGCs located outside the hex guard were found to be significantly (>2 fold) higher than those located inside the area of tissue bounded by the hex guard. The hexapolar configuration localized the activation of RGCs more effectively than its monopolar counterpart.

Furthermore, no difference in hexapolar thresholds or localization was observed when using cathodic-first versus anodic-first stimulation.

Significance: The hexapolar configuration may provide an improved method for electrically stimulating spatially distinct populations of cells in retinal tissue.

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Retina. 2013 Apr 19. [Epub ahead of print]

EFFECTS OF VITREOMACULAR ADHESION ON ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR TREATMENT FOR POLYPOIDAL CHOROIDAL VASCULOPATHY.

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PURPOSE: To evaluate the effect of posterior vitreomacular adhesion (VMA), documented by optical coherence tomography, on the outcome of anti-vascular endothelial growth factor treatment of polypoidal choroidal vasculopathy.

METHODS: Medical records of 102 patients (104 eyes) with polypoidal choroidal vasculopathy were retrospectively reviewed and categorized according to the presence of posterior VMA into 2 subgroups: VMA positive (+) group (23 eyes) and VMA negative (-) group (81 eyes). Best-corrected visual acuity and central macular thickness after antivascular endothelial growth factor treatment were compared between the 2 groups at baseline and at 1 month, 3 months, 6 months, and 12 months.

RESULTS: At the last follow-up, average number of injections was 4.82 ± 1.27 in the VMA (+) group and 4.92 ± 1.45 in the VMA (-) group. After injection, the mean logarithm of the minimum angle of resolution of best-corrected visual acuity improved from 0.81 ± 0.53 (Snellen equivalent, 20/129) to 0.67 ± 0.52 (Snellen equivalent, 20/93) in the VMA (+) group ($P = 0.01$) and from 0.79 ± 0.50 (Snellen equivalent, 20/123) to 0.64 ± 0.58 (Snellen equivalent, 20/91) in the VMA (-) group ($P = 0.02$). Average central macular thickness decreased from $354.4 \pm 124.5 \mu\text{m}$ to $249.6 \pm 112.5 \mu\text{m}$ in the VMA (+) group ($P = 0.01$) and from $361.2 \pm 140.2 \mu\text{m}$ to $267.3 \pm 103.5 \mu\text{m}$ in the VMA (-) group ($P = 0.01$). Polyp regression rate was 21.7% (5 eyes of 23 eyes) in the VMA (+) group and 22.2% (18 eyes of 81 eyes) in the VMA (-) group. There was no statistically significant difference in the best-corrected visual acuity improvement, central macular thickness improvement, and polyp regression rate between the groups.

CONCLUSION: Unlike typical age-related macular degeneration, posterior VMA was not associated with a visual outcome after intravitreal antivascular endothelial growth factor for polypoidal choroidal vasculopathy.

PMID: 23609123 [PubMed - as supplied by publisher]

Trends Neurosci. 2013 Apr 16. pii: S0166-2236(13)00053-2. doi: 10.1016/j.tins.2013.03.006. [Epub ahead of print]

Development of human embryonic stem cell therapies for age-related macular degeneration.

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Abstract: Age-related macular degeneration (AMD) is the leading cause of vision loss in older adults and

ultimately leads to the death of photoreceptor cells in the macular area of the neural retina. Currently, treatments are only available for patients with the wet form of AMD. In this review, we describe recent approaches to develop cell-based therapies for the treatment of AMD. Recent research has focused on replacing the retinal pigment epithelium (RPE), a monolayer of cells vital to photoreceptor cell health. We discuss the various methods used to differentiate and purify RPE from human embryonic stem cells (HESC), and describe the surgical approaches being used to transplant these cells in existing and forthcoming clinical trials.

PMID: 23601133 [PubMed - as supplied by publisher]

Sichuan Da Xue Xue Bao Yi Xue Ban. 2013 Jan;44(1):68-71.

**[Ocular higher-order aberrations in patients with neovascular age-related macular degeneration].
[Article in Chinese]**

Tan Q, Zhang M, Liu LQ.

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OBJECTIVE: To evaluate changes in higher-order aberrations of eyes in patients with unilateral neovascular age-related macular degeneration (nAMD).

METHODS: Thirty two patients with unilateral nAMD were recruited for this study. Biocular higher-order wavefront aberrations for a 6-mm pupil were measured with Zywave II aberrometer (Bausch & Lomb, Zyoptix, USA). The root mean square (RMS) of Zernike coefficients were compared between the eyes with nAMD and the fellow eyes. Relation ship between RMS values and LogMAR vision of the nAMD were analysed.

RESULTS: The total higher-order aberrations (HOAs), third order aberrations (RMS3), sphere aberration (SA), coma, coma along x axis, and horizontal trefoil in the eyes with nAMD were all significantly greater than those in the fellow eyes ($P < 0.05$). Increases of vertical trefoil and coma were found to be associated with increased LogMAR values ($r(s) = 0.377$, $P = 0.034$; $r(s) = 0.416$, $P = 0.018$).

CONCLUSION: Higher-order aberrations in nAMD are greater than normal eyes, which may have effects on distant corrected visual acuity. Examinations of higher-order aberrations should be added into visual function evaluations of nAMD.

PMID: 23600213 [PubMed - in process]

Retina. 2013 Apr 19. [Epub ahead of print]

FEASIBILITY OF A NOVEL REMOTE DAILY MONITORING SYSTEM FOR AGE-RELATED MACULAR DEGENERATION USING MOBILE HANDHELD DEVICES: Results of a Pilot Study.

Kaiser PK, Wang YZ, He YG, Weisberger A, Wolf S, Smith CH.

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PURPOSE: This pilot study evaluated the feasibility of the Health Management Tool (HMT), a novel computing system using mobile handheld devices, to remotely monitor retinal visual function daily in patients with neovascular age-related macular degeneration treated with ranibizumab.

METHODS: Patients with neovascular age-related macular degeneration in at least 1 eye (newly diagnosed or successfully treated < 1 year) and eligible for ranibizumab therapy were enrolled in this 16-week, prospective, open-label, single-arm study. Patients performed a shape discrimination hyperacuity test (myVisionTrack [mVT]) daily on the HMT device (iPhone 3GS) remotely and at all clinic visits. Data entered into HMT devices were collected in the HMT database, which also sent reminders for patients to take mVT.

RESULTS: Among 160 patients from 24 U.S. centers enrolled in the study (103 [64%] ≥75 years of age), 84.7% on average complied with daily mVT testing and ~98.9% complied with at least weekly mVT testing. The HMT database successfully uploaded more than 17,000 mVT assessment values and sent more than 9,000 reminders.

CONCLUSION: Elderly patients with neovascular age-related macular degeneration were willing and able to comply with daily self-testing of retinal visual function using mobile handheld devices in this novel system of remote vision monitoring.

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Pathogenesis

Eur Cytokine Netw. 2013 Apr 22. [Epub ahead of print]

Contribution of TNF- α to the development of retinal neurodegenerative disorders.

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Abstract: During the late 1970s, tumor necrosis factor alpha (TNF- α) was initially recognized as an endotoxin-induced substance that was mainly produced by macrophages, and able to cause the lysis of certain tumor cells. Subsequent research demonstrated that TNF- α mediates a broad range of cellular activities, including proliferation, survival, differentiation and apoptosis. It is also considered to be essential for the induction and maintenance of the inflammatory immune responses. Meanwhile, visual impairment imposes a substantial disease burden on society. It is associated with both significant economic impact and reduction in quality of life. Visual impairment raises serious social challenges for both patients and their families, interfering with day-to-day life, and can limit employment possibilities. Many of the most common, irreversible blinding pathologies involve neuronal loss from the retina, which is the light-sensing tissue of the eye. The retina, being part of the central nervous system, is unable to regenerate neurons lost to disease. Therefore, in the current review we will discuss the association between increased expression of TNF- α with neurodegenerative disorders, downstream cellular signaling mechanisms following interaction of TNF- α with its receptors, and the role of TNF- α as a possible target in the treatment of retinal neurodegenerative disorders.

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Mol Pharm. 2013 Apr 22. [Epub ahead of print]

Hypoxia Alters Ocular Drug Transporter Expression and Activity in Hypoxic Rat and Calf Models: Implications for Drug Delivery.

Kadam RS, Ramamoorthy P, Laflamme DJ, McKinsey TA, Kompella UB.

Purpose: Hypoxia, a key stimulus for neovascularization, has been implicated in the pathology of

proliferative diabetic retinopathy, retinopathy of prematurity and wet age related macular degeneration. The aim of the present study was to determine the effect of hypoxia on drug transporter mRNA expression and activity in ocular barriers.

Methods: Sprague Dawley rats were exposed to hypobaric hypoxia (PB = 380 mm Hg) for 6 weeks and neonatal calves were maintained under hypobaric hypoxia (PB = 445 mm Hg) for 2 weeks. Age matched controls for rats and calves were maintained at ambient altitude and normoxia. The effect of hypoxia on transporter expression was analyzed by qRT-PCR analysis of transporter mRNA expression in hypoxic and control rat choroid-retina. Effect of hypoxia on the activity of PEPT, OCT, ATB0+, and MCT transporters was evaluated using in vitro transport studies of model transporter substrates across calf cornea and sclera -choroid-RPE (SCRPE).

Results: Quantitative gene expression analysis of 84 transporters in rat choroid-retina showed ≥ 1.5 -fold up regulation or down regulation of 29 transporter genes during hypoxia. Nine out of 29 ATP binding cassette (ABC) families of efflux transporters including MRP3, MRP4, MRP5, MRP6, MRP7, Abca17, Abc2, Abc3, and RGD1562128 were up regulated. For solute carrier family transporters, 11 transporters including SLC10a1, SLC16a3, SLC22a7, SLC22a8, SLC29a1, SLC29a2, SLC2a1, SLC3a2, SLC5a4, SLC7a11, and SLC7a4 were up regulated, while 4 transporters including SLC22a2, SLC22a9, SLC28a1, and SLC7a9 were down regulated in hypoxia. Of the 3 aquaporin (Aqp) water channels, Aqp-9 was down regulated and Aqp-1 was up regulated during hypoxia. Gene expression analysis showed down regulation of OCT-1, OCT-2, and ATB0+ and up regulation of MCT-3 in hypoxic rat choroid-retina, without any effect on the expression of PEPT-1 and PEPT-2 expression. Functional activity assays of PEPT, OCT, ATB0+, and MCT transporters in calf ocular tissues showed that PEPT, OCT, and ATB0+ functional activity was down regulated, whereas MCT functional activity was up regulated in hypoxic cornea and SCRPE. Gene expression analysis of these transporters in rat tissues was consistent with the functional transport assays except for PEPT transporters.

Conclusions: Hypoxia results in significant alterations in the mRNA expression and functional activity of solute transporters in ocular tissues.

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Graefes Arch Clin Exp Ophthalmol. 2013 Apr 20. [Epub ahead of print]

Factor Xa and thrombin stimulate proinflammatory and profibrotic mediator production by retinal pigment epithelial cells: a role in vitreoretinal disorders?

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BACKGROUND: Vitreoretinal disorders, including proliferative vitreoretinopathy (PVR), proliferative diabetic retinopathy (PDR) and exudative age-related macular degeneration (AMD), are a major cause of visual impairment worldwide and can lead to blindness when untreated. Loss of blood-retinal barrier (BRB) integrity associated with vitreoretinal fibrin deposition, inflammation, fibrosis and neovascularization contribute to the pathophysiological processes in these disorders. Retinal pigment epithelial (RPE) cells are well recognized to contribute to vitreoretinal inflammation/fibrosis and are likely to encounter contact with coagulation factor upon loss of BRB integrity.

METHODS: An extensive study was performed in which we examined the effect of factor Xa and thrombin on the production of a broad panel of cytokines/chemokines and growth factors by RPE cells. For this purpose we used the ARPE-19 cell line as well as primary RPE cells, a glass slide based array that allows simultaneous detection of 120 cytokines/chemokines and growth factors, ELISA and real-time-quantitative PCR. The involved signaling cascade was examined using specific inhibitors for protease activated

receptor (PAR)1, PAR2 and nuclear factor kappa-B (NF-κB).

RESULTS: Factor Xa and thrombin regulated the production of cytokines and growth factors (including GM-CSF, IL-6, IL-8, MCP-3, PDGF-AA, PDGF-BB, TIMP-1 and TGF-α) that fit well in the pathobiology of vitreoretinal disease. Blocking studies revealed that the effects were mediated via PAR1 induced NF-κB activation.

CONCLUSIONS: Our findings suggest that factor Xa and thrombin can drive vitreoretinal inflammation and fibrosis and should be considered as treatment targets in vitreoretinal disorders such as PVR, PDR and AMD.

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Int J Biochem Cell Biol. 2013 Apr 17. pii: S1357-2725(13)00118-0. doi: 10.1016/j.biocel.2013.04.013. [Epub ahead of print]

Cellular and molecular mechanisms of age-related macular degeneration: From impaired autophagy to neovascularization.

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Abstract: Age-related macular degeneration (AMD) is a complex, degenerative and progressive disease involving multiple genetic and environmental factors. It can result in severe visual loss e.g. AMD is the leading cause of blindness in the elderly in the western countries. Although age, genetics, diet, smoking, and many cardiovascular factors are known to be linked with this disease there is increasing evidence that long-term oxidative stress, impaired autophagy clearance and inflammasome mediated inflammation are involved in the pathogenesis. Under certain conditions these may trigger detrimental processes e.g. release of vascular endothelial growth factor (VEGF), causing choroidal neovascularisation e.g. in wet AMD. This review ties together these crucial pathological threads in AMD.

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Parainflammation associated with advanced glycation endproduct stimulation of RPE in vitro: Implications for age-related degenerative diseases of the eye.

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Abstract: Age related macular degeneration (AMD) is one of the leading causes of blindness in Western society. A hallmark of early stage AMD are drusen, extracellular deposits that accumulate in the outer retina. Advanced glycation endproducts (AGE) accumulate with aging and are linked to several age-related diseases such as Alzheimer's disease, osteoarthritis, atherosclerosis and AMD. AGE deposits are found in drusen and in Bruch's membrane of the eye and several studies have suggested its role in promoting oxidative stress, apoptosis and lipofuscin accumulation. Recently, complement activation and chronic inflammation have been implicated in the pathogenesis of AMD. While AGEs have been shown to promote inflammation in other diseases, whether it plays a similar role in AMD is not known. This study investigates the effects of AGE stimulation on pro- and anti-inflammatory pathways in primary culture of human retinal pigment epithelial cells (RPE). Differential gene expression studies revealed a total of 41 up- and 18 down-

regulated RPE genes in response to AGE stimulation. These genes fell into three categories as assessed by gene set enrichment analysis (GSEA). The main categories were inflammation (interferon-induced, immune response) and proteasome degradation, followed by caspase signaling. Using suspension array technology, protein levels of secreted cytokines and growth factors were also examined. Anti-inflammatory cytokines including IL10, IL1ra and IL9 were all overexpressed. Pro-inflammatory cytokines including IL4, IL15 and IFN- γ were overexpressed, while other pro-inflammatory cytokines including IL8, MCP1, IP10 were underexpressed after AGE stimulation, suggesting a para-inflammation state of the RPE under these conditions. Levels of mRNA of chemokine, CXCL11, and viperin, RSAD2, were up-regulated and may play a role in driving the inflammatory response via the NF- κ B and JAK-STAT pathways. CXCL11 was strongly immunoreactive and associated with drusen in the AMD eye. The pathways and novel genes identified here highlight inflammation as a key response to AGE stimulation in primary culture of human RPE, and identify chemokine CXCL11 as putative novel agent associated with the pathogenesis of AMD.

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[Etiology and pathogenesis of age-related macular degeneration].

[Article in German]

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Abstract: Age-related macular degeneration (AMD) is the most common cause of blindness in Germany. Due to the demographic development a further increase of affected patients is to be expected. Improved understanding of AMD pathogenesis resulted from the molecular biological approaches in recent years and showed an association of genetic factors with AMD. The complement factor H gene and the second high-risk locus ARMS2 in particular were found to contribute a significant risk for development of the disease. Ageing and environmental factors, such as smoking, modulate the individual genetic risk profile. A detailed understanding of the complex AMD pathogenesis is also relevant in ophthalmological practice to understand new treatment strategies. In this review we aim to give an overview of the interplay of ageing, external environmental factors and genetic risk variants leading to AMD.

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Genetics

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Gene expression changes in aging retinal microglia: relationship to microglial support functions and regulation of activation.

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Abstract: Microglia, the resident immune cells of the central nervous system (CNS), are thought to contribute to the pathogenesis of age-related neurodegenerative disorders. It has been hypothesized that microglia undergo age-related changes in gene expression patterns that give rise to pathogenic

phenotypes. We compared the gene expression profiles in microglia isolated ex vivo from the retinas of mice ranging from early adulthood to late senescence. We discovered that microglial gene expression demonstrated progressive change with increasing age, and involved genes that regulate microglial supportive functions and immune activation. Molecular pathways involving immune function and regulation, angiogenesis, and neurotrophin signaling demonstrated age-related change. In particular, expression levels of complement genes, C3 and CFB, previously associated with age-related macular degeneration (AMD), increased with aging, suggesting that senescent microglia may contribute to complement dysregulation during disease pathogenesis. Taken together, senescent microglia demonstrate age-related gene expression changes capable of altering their constitutive support functions and regulation of their activation status in ways relating to neuroinflammation and neurodegeneration in the CNS.

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