Macular Disease Foundation AUSTRALIA
Our focus is your vision

MD Research News

Issue 176

Monday 14 April, 2014

This free weekly bulletin lists the latest published research articles on macular degeneration (MD) and some other macular diseases as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases.

If you have not already subscribed, please email Rob Cummins at **research@mdfoundation.com.au** with 'Subscribe to MD Research News' in the subject line, and your name and address in the body of the email.

You may unsubscribe at any time by an email to the above address with your 'unsubscribe' request.

Drug treatment

Graefes Arch Clin Exp Ophthalmol. 2014 Apr 11. [Epub ahead of print]

Factors influencing the exudation recurrence after cataract surgery in patients previously treated with anti-vascular endothelial growth factor for exudative age-related macular degeneration.

Lee TG, Kim JH, Chang YS, Kim CG, Kim JW.

PURPOSE: To investigate factors influencing exudation recurrence following cataract surgery in patients already treated with anti-vascular endothelial growth factor (VEGF) agents for exudative age-related macular degeneration (AMD).

METHODS: A retrospective review of medical records was performed for patients who underwent cataract surgery and had been previously treated with anti-VEGF for exudative AMD. Visual acuity was examined before surgery and 1 and 6 months after surgery. The time between diagnosis and surgery, and the exudation-free period before surgery were examined and compared between patients who had exudation recurrence and those that did not.

RESULTS: Thirty-nine eyes of 39 patients were included in analyses. The logarithm of the minimum angle of resolution visual acuity was 1.02 ± 0.58 and had significantly improved 1 month (0.81 ± 0.62, P < 0.001) and 6 months (0.85 ± 0.64, P = 0.001) following surgery. Both the diagnosis-to-surgery period (P = 0.001) and the preoperative exudation-free period (P < 0.001) were significantly longer in patients without recurrence than in patients with recurrence.

CONCLUSIONS: Cataract surgery was beneficial in patients previously treated with anti-VEGF for exudative AMD. Our data suggests that cataract surgery should be performed after a sufficiently long exudation-free period to minimize exudation recurrence. But larger prospective studies are required to draw definitive clinical guidelines.

PMID: 24723165 [PubMed - as supplied by publisher]

Eye (Lond). 2014 Apr 11. doi: 10.1038/eye.2014.64. [Epub ahead of print]

Switch of anti-VEGF agents is an option for nonresponders in the treatment of AMD.

Ehlken C, Jungmann S, Böhringer D, Agostini HT, Junker B, Pielen A; Medscape.

Background: Although anti-VEGF therapy of exudative AMD with bevacizumab and ranibizumab proved

efficacious in the majority of patients, CNV activity does not respond to continued treatment after repeated injections in a considerable amount of patients. These are referred to as nonresponders. A change of the drug to bevacizumab or ranibizumab could possibly offer an alternative option for the treatment of nonresponding exudative AMD.

Methods and materials: A total of 138 nonresponders who switched therapy from bevacizumab to ranibizumab (n=114) or vice versa (n=24) were included in a retrospective study. Visual acuity (VA) and foveal thickness before and after the switch of therapy were compared. By means of linear regression analysis, we analyzed possible prognostic factors associated with a favorable outcome for visual acuity.

Results: Linear regression analysis revealed a statistically significant benefit for nonresponders when treatment was changed to a different anti-VEGF drug (bevacizumab or ranibizumab). VA at the time of the switch was positively correlated with a beneficial development of VA after changing the drug. There was no significant correlation with age, macular thickness, number of injections before the switch, or the development of VA under treatment before the switch. Both patients switching to Avastin and Lucentis benefitted without statistically significant differences.

Conclusions: An exchange of bevacizumab with ranibizumab or vice versa should be considered in nonresponders in the treatment of exudative AMD. Further prognostic factors may help to identify patients who might benefit from a switch. These factors should be investigated in further studies.Eye advance online publication, 11 April 2014; doi:10.1038/eye.2014.64.

PMID: 24722504 [PubMed - as supplied by publisher]

Eur J Ophthalmol. 2014 Mar 17:0. doi: 10.5301/ejo.5000421. [Epub ahead of print]

Initial utilization of aflibercept in exudative age-related macular degeneration.

Cho H, Weber ML, Shah CP, Heier JS.

Purpose: Intravitreal aflibercept, a fusion protein with high affinity for vascular endothelial growth factor, offers an alternative treatment for exudative age-related macular degeneration. Preclinical studies and early and late phase clinical trials suggest that aflibercept's high binding affinity may impart greater durability of activity and increased efficacy compared to ranibizumab or bevacizumab.

Methods: A total of 266 eyes of 249 patients with exudative age-related macular degeneration who received aflibercept after treatment with bevacizumab and/or ranibizumab were included in a retrospective review. Mean central subfoveal thickness on spectral-domain optical coherence tomography and mean logarithm of the minimal angle of resolution (logMAR) visual acuity were calculated at 1, 3, 6, and 12 months after the first aflibercept injection. Subgroup analyses were performed in eyes receiving at least 5 bevacizumab and/or ranibizumab injections in the 6 months prior to aflibercept and in eyes receiving at least 10 injections in the 12 months prior to aflibercept.

Results: Eyes received an average of 14.7 (range 1-43) ranibizumab and/or bevacizumab treatments prior to initiation of aflibercept therapy. The mean central subfoveal thickness decreased from 300 to 275 µm at 1 month (p<0.001) and was maintained at 6 months. Mean logMAR visual acuity improved from 0.60 (Snellen equivalent 20/80) to 0.54 (20/70, p = 0.01) at 1 month and was stable at 0.55 at 6 months (Snellen equivalent 20/70, p = 0.11, n = 251). In 82 eyes receiving at least 5 injections in the 6 months prior to aflibercept treatment (average of 18.1 injections total), the central subfoveal thickness improved from 296 to 279 µm at 1 month (p<0.0001) and was maintained at 6 months (p<0.0001). Visual acuity did not change (0.48 [20/61] at 1 month compared to baseline, 0.49 [20/62], p = 0.634, and at 6 months 0.51 [20/65], p = 0.601). In 50 eyes receiving at least 10 injections in the 12 months prior to aflibercept treatment (average of 21.8 injections total), the mean central subfoveal thickness decreased by 17 µm at 1 month (p = 0.0007) and was maintained at 6 months (p = 0.013). Again, visual acuity did not change (0.46 [20/56] at 1 month, baseline 0.44 [20/56], p = 0.547, and 0.50 [20/63] at 6 months, p = 0.2445).

Conclusions: Aflibercept is a valuable treatment alternative in patients previously treated with bevacizumab and/or ranibizumab injections. Stability of visual acuity and anatomic improvement on spectral-domain optical coherence tomography were observed after initiation of aflibercept treatment in those preciously treated with ranibizumab and/or bevacizumab injections every 4-6 weeks.

PMID: 24706352 [PubMed - as supplied by publisher]

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

Bimonthly injections of ranibizumab for age-related macular degeneration.

Sawada T, Kakinoki M, Wang X, Kawamura H, Saishin Y, Ohji M.

PURPOSE: To evaluate the efficacy of bimonthly intravitreal injections of ranibizumab for age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV) in a pilot study.

METHODS: This study was a prospective, interventional case series. Thirty eyes of 30 patients received prospectively at least three bimonthly intravitreal injections of ranibizumab (0.5 mg/0.05 ml) without loading doses. The best-corrected visual acuity (BCVA) and the central retinal subfield thickness (CRST) were measured before and monthly after the injections.

RESULTS: Twenty-eight patients received the three planned injections; one patient refused the third injection, one patient did not receive the third injection because blood pressure was raised, and one patient received a rescue injection at month 5 because of increased retinal thickness. The mean logarithm of the minimum angle of resolution (logMAR) BCVA was 0.44 ± 0.37 before treatment and significantly improved to 0.25 ± 0.34 at month 6 ($p < 0.001$). The mean CRST was 335 ± 85.9 μm before treatment and decreased significantly to 261 ± 78.1 μm at month 6 ($p < 0.001$). Nine of 30 patients received six planned injections for 12 months. The mean logMAR BCVA was 0.38 ± 0.39 before treatment and significantly improved to 0.18 ± 0.33 at month 12 ($p = 0.005$). The mean CRST was 360 ± 110.8 μm before treatment and decreased significantly to 249 ± 57.0 μm at month 12 ($p = 0.025$).

CONCLUSIONS: Bimonthly injections of ranibizumab may be effective for treating AMD and PCV.

PMID: 24705851 [PubMed - as supplied by publisher]

Ophthalmic Surg Lasers Imaging Retina. 2014 Apr 11:1-5. doi: 10.3928/23258160-20140404-01. [Epub ahead of print]

Treat-and-Extend Intravitreal Bevacizumab for Branch Retinal Vein Occlusion.

Rush RB, Simunovic MP, Aragon AV 2nd, Ysasaga JE.

BACKGROUND AND OBJECTIVE: To determine the effectiveness and direct medical costs of treat-and-extend (TAE) intravitreal bevacizumab (IVB) for the treatment of branch retinal vein occlusion (BRVO)-associated macular edema (ME).

PATIENTS AND METHODS: Retrospective chart review of 52 consecutive patients diagnosed with BRVO-associated ME treated with IVB using a TAE protocol.

RESULTS: Mean change in logMAR vision was -0.30 ($P < .001$), and mean change in central macular thickness was -244.0 μm ($P < .001$). The mean number of injections was 8.2 (95% CI; 7.8 to 8.6). The yearly average direct cost of the TAE regimen was calculated to be $2,580.26 per patient.

CONCLUSION: Treatment of BRVO-associated ME with IVB using a TAE regimen resulted in similar visual outcomes and number of intravitreal injections as did as-needed treatment with 0.5 mg ranibizumab

conducted in phase 3 trials but with fewer visits and lower annual medical costs. [Ophthalmic Surg Lasers Imaging Retina. 2014;45:xxx-xxx.].

PMID: 24716783 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2014 Apr 7. doi: 10.1136/bjophthalmol-2013-304670. [Epub ahead of print]

Predictive factors for non-response to intravitreal ranibizumab treatment in age-related macular degeneration.

Suzuki M, Nagai N, Izumi-Nagai K, Shinoda H, Koto T, Uchida A, Mochimaru H, Yuki K, Sasaki M, Tsubota K, Ozawa Y.

BACKGROUND/AIMS: To study the initial characteristics and response to intravitreal ranibizumab (IVR) treatment of age-related macular degeneration (AMD).

METHODS: We reviewed the clinical records of 141 eyes in 141 AMD patients who received monthly IVR for 3 months and thereafter pro re nata (PRN) injections for 9 months as the first treatment for AMD. Patients whose best corrected visual acuity (BCVA) worsened at month 12, and those with increased exudative fundus findings after IVR or an increased central retinal thickness of more than 100 μm at month 12, were considered to be non-responders as judged by BCVA and fundus findings, respectively. Non-responders' initial characteristics were analysed using logistic regression models.

RESULTS: 14.9% of eyes were non-responders as judged by BCVA, and 17.0% were non-responders as judged by fundus findings. Initial fibrovascular pigment epithelial detachment (PED) (OR 22.9, 95% CI 2.61 to 201) and serous PED (OR 4.12, 95% CI 1.08 to 15.8) were associated with non-response as judged by BCVA. Initial fibrovascular PED (OR 33.5, 95% CI 2.95 to 381) and type 1 choroidal neovascularization (OR 6.46, 95% CI 1.39 to 30.0) were associated with non-response, as judged by fundus findings.

CONCLUSIONS: Although most AMD responded to IVR, non-responders had initial clinical characteristics that might be informative for managing their treatment.

PMID: 24711658 [PubMed - as supplied by publisher]

Mayo Clin Health Lett. 2013 Sep;31(9):1-3.

Macular degeneration. Early treatment important.

[No authors listed]

PMID: 24719959 [PubMed - in process]

Other treatment & diagnosis

Klin Monbl Augenheilkd. 2014 Apr 8. [Epub ahead of print]

[Full Depth Imaging: a New Imaging Technique Using Optical Coherence Tomography (OCT).] [Article in German]

Celik N, Pollithy S, Dithmar S.

Purpose: The aim of this study was to evaluate the full depth imaging (FDI) mode as a new acquisition technique with spectral domain (SD) optical coherence tomography (OCT) from Heidelberg Engineering for illustrating vitreoretinal and choroidal structures with high contrast.

Methods: Patients with different diseases such as age-related macular degeneration, chorioretinopathia centralis serosa, diabetic retinopathy and epiretinal gliosis were examined with the FDI mode. For comparison, we also examined healthy probands with conventional OCT and the enhanced depth imaging (EDI) mode. FDI images were obtained with a manual acquisition technique. First, 100 conventional OCT scans of the vitreoretinal interface were averaged. After manual switching to the EDI mode the previous averaged image was overlayed with EDI images until vitreous, retina and choroid were projected in one comparably sharp image.

Results: The FDI mode enables SD-OCT images showing the vitreoretinal interface and deep choroid structures with a high contrast. The new acquisition mode has a few limitations: it is only possible to perform a single linear scan, a raster scan is not possible. The FDI mode is a manual acquisition technique and not automated yet.

Conclusion: By a combination of averaged images of the vitreoretinal interface with the help of conventional SD-OCT scans with EDI OCT scans the FDI mode exhibits a simultaneous contrasty image of the posterior vitreous, the retina and the choroid. Whereas the application of OCT was focused to evaluate the retina-retinal pigment epithel complex, the routine reinforcement of FDI scans could additionally show potential vitreous and choroidal pathologies. As the FDI mode is not an automated application yet it may be too complex to use for routine diagnostics at the moment.

PMID: 24715408 [PubMed - as supplied by publisher]

Optom Vis Sci. 2014 Apr 3. [Epub ahead of print]

Twelve-Month Natural History of Dark Adaptation in Patients with AMD.

Jackson GR, Clark ME, Scott IU, Walter LE, Quillen DA, Brigell MG.

PURPOSE: A sensitive endpoint is required for clinical trials evaluating preventative therapies for early age-related macular degeneration (AMD). Dark adaptation (DA) is a sensitive marker of AMD and has been proposed as a potential endpoint. This study evaluated whether significant changes in DA speed could be detected in participants with early to intermediate AMD at 12 months following baseline DA measurement.

METHODS: Dark adaptation, visual acuity (VA), and fundus photography were obtained at baseline and at 6 and 12 months in 26 subjects with AMD and in 6 subjects with normal retinal health. Disease severity was assessed by the Nine-Step Age-Related Eye Disease Study AMD severity scale.

RESULTS: At 12 months, significant progression of DA impairment occurred in 5 of 26 (19%) participants with AMD. None of the participants with AMD exhibited a significant worsening of fundus grade or decrease of acuity related to disease progression. The normal group exhibited stable DA and VA during the observation period.

CONCLUSIONS: Significant worsening of DA was observed in 19% of subjects with AMD in 12 months of observation, despite stable VA and fundus appearance. This study suggests that DA may be a suitable functional endpoint for early clinical studies evaluating novel treatments for early to intermediate AMD.

PMID: 24705482 [PubMed - as supplied by publisher]

C R Biol. 2014 Mar;337(3):214-22. doi: 10.1016/j.crvi.2014.01.001. Epub 2014 Feb 26.

Retinal prostheses: Clinical results and future challenges.

Picaud S, Sahel JA.

Abstract: Retinal prostheses aim at restoring visual perception in blind patients affected by retinal diseases

leading to the loss of photoreceptors, such as age-related macular degeneration or retinitis pigmentosa. Recent clinical trials have demonstrated the feasibility of this approach for restoring useful vision. Despite a limited number of electrodes (60), and therefore of pixels, some patients were able to read words and to recognize high-contrast objects. Face recognition and independent locomotion in unknown urban environments imply technological breakthroughs to increase the number and density of electrodes. This review presents recent clinical results and discusses future solutions to answer the major technological challenges.

PMID: 24702848 [PubMed - in process]

Semin Ophthalmol. 2014 Apr 4. [Epub ahead of print]

Suicide and Visual Loss: A Case Report Reflecting the Need for Recognition and Management in Ophthalmological Settings.

Johnson T, Rovner B, Haller J.

Abstract: In the United States, 5.5 million people over the age of 40 meet criteria for visual impairment (VI). They often suffer significant psychosocial and health consequences, including reduced quality of life and depression, which can be persistent and difficult to treat. Additionally, VI may increase the risk of suicide. We report a case of a patient with age-related macular degeneration (ARMD) and suicidal ideation. While this link is reasonable, there are no prior cases of suicidality among patients with ARMD. Moreover, the literature is silent regarding proper approaches to diagnosing and managing suicidality among patients with VI, especially ARMD.

PMID: 24702438 [PubMed - as supplied by publisher]

Mayo Clin Health Lett. 2013 May;31(5):8.

As my eyesight has gotten worse from macular degeneration, I've started to see hallucinations of people. I know they're not real, but I'm worried this may be the start of Alzheimer's. Are there other explanations?

[No authors listed]

PMID: 24701650 [PubMed - in process]

ISRN Ophthalmol. 2014 Jan 22;2014:417603. doi: 10.1155/2014/417603. eCollection 2014.

Phacoemulsification surgery in eyes with neovascular age-related macular degeneration.

Grixti A, Papavasileiou E, Cortis D, Kumar BV, Prasad S.

Purpose: To evaluate the visual outcomes and effect of phacoemulsification surgery on the progression of neovascular age-related macular degeneration (AMD).

Methods: Retrospective, noncomparative, and interventional case series. Thirty eyes from 29 subjects with neovascular AMD treated with intravitreal antivascular endothelial growth factor (VEGF) injections who underwent phacoemulsification and had a postsurgery follow-up of 6 months were included. LogMAR best corrected visual acuity (BCVA) was assessed preoperatively; 1 month, 3 months, and 6 months postoperatively; and finally at the last visit. The frequency of anti-VEGF therapy, calculated as the number of intravitreal injections per month, and central macular thickness (CMT) before and after cataract surgery were determined.

Results: Median (range) logMAR BCVA was 0.69 (0.16 to 1.32) preoperatively; 0.55 (-0.04 to 1.32) at 1 month, 0.52 (-0.1 to 1.32) at 3 months, and 0.50 (0.0 to 1.32) at 6 months postoperatively; and 0.6 (0.0 to 1.4) at final visit (P = 0.0011). There was no difference in the frequency of anti-VEGF injections between the immediate 6 months before and after phacoemulsification, which was equal to 0.1667 injections per month (P = 0.6377). Median CMT measured 203 μ m preoperatively, which temporarily increased to 238 μ m at 1 month after surgery (P = 0.0093) and then spontaneously returned to baseline, measuring 212.5 μ m at 3 months postoperatively (P = 0.3811).

Conclusion: Phacoemulsification surgery significantly improved vision in patients with neovascular AMD, with no increased need for anti-VEGF injections to keep the macula dry postoperatively.

PMID: 24719771 [PubMed]

Pathogenesis

Drug Discov Today. 2014 Apr 6. pii: S1359-6446(14)00120-2. doi: 10.1016/j.drudis.2014.03.026. [Epub ahead of print]

Epigenetic modifications as potential therapeutic targets in age-related macular degeneration and diabetic retinopathy.

Kwa FA, Thrimawithana TR.

Abstract: Recently, aberrant epigenetic modifications have been identified in the pathogenesis of the posterior eye diseases, age-related macular degeneration (AMD) and diabetic retinopathy (DR). This has led to the development of alternative therapies that can alter aberrant chromatin-remodelling processes involved in AMD and DR. These novel therapeutic agents could help to ameliorate the challenges associated with current treatments that are limited by variable patient response and disease heterogeneity. However, research on the use of epigenetic-based therapies in these diseases is relatively young and, therefore, preclinical studies that evaluate their mechanism of action, specificity and adverse effects are warranted.

PMID: 24717156 [PubMed - as supplied by publisher]

PLoS One. 2014 Apr 8;9(4):e94313. doi: 10.1371/journal.pone.0094313. eCollection 2014.

VEGF-Production by CCR2-Dependent Macrophages Contributes to Laser-Induced Choroidal Neovascularization.

Krause TA, Alex AF, Engel DR, Kurts C, Eter N.

Abstract: Age-related macular degeneration (AMD) is the most prevalent cause of blindness in the elderly, and its exsudative subtype critically depends on local production of vascular endothelial growth factor A (VEGF). Mononuclear phagocytes, such as macrophages and microglia cells, can produce VEGF. Their precursors, for example monocytes, can be recruited to sites of inflammation by the chemokine receptor CCR2, and this has been proposed to be important in AMD. To investigate the role of macrophages and CCR2 in AMD, we studied intracellular VEGF content in a laser-induced murine model of choroidal neovascularisation. To this end, we established a technique to quantify the VEGF content in cell subsets from the laser-treated retina and choroid separately. 3 days after laser, macrophage numbers and their VEGF content were substantially elevated in the choroid. Macrophage accumulation was CCR2-dependent, indicating recruitment from the circulation. In the retina, microglia cells were the main VEGF+ phagocyte type. A greater proportion of microglia cells contained VEGF after laser, and this was CCR2-independent. On day 6, VEGF-expressing macrophage numbers had already declined, whereas numbers of VEGF+ microglia cells remained increased. Other sources of VEGF detectable by flow cytometry included in

dendritic cells and endothelial cells in both retina and choroid, and Müller cells/astrocytes in the retina. However, their VEGF content was not increased after laser. When we analyzed flatmounts of laser-treated eyes, CCR2-deficient mice showed reduced neovascular areas after 2 weeks, but this difference was not evident 3 weeks after laser. In summary, CCR2-dependent influx of macrophages causes a transient VEGF increase in the choroid. However, macrophages augmented choroidal neovascularization only initially, presumably because VEGF production by CCR2-independent eye cells prevailed at later time points. These findings identify macrophages as a relevant source of VEGF in laser-induced choroidal neovascularization but suggest that the therapeutic efficacy of CCR2-inhibition might be limited.

PMID: 24714223 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2014 Apr 8. pii: iovs.13-13659v1. doi: 10.1167/iovs.13-13659. [Epub ahead of print]

Aberrant Cell and Basement Membrane Architecture Contribute to Sidestream Smoke-Induced Choroidal Endothelial Dysfunction.

Yang X, Scott HA, Ardekani S, Williams M, Talbot P, Ghosh K.

Purpose: Environmental tobacco smoke (ETS) is widely regarded as a major modifiable risk factor for age-related macular degeneration (AMD). Yet, precisely how it exerts its pathological effects is poorly understood. Since early-stage AMD is characterized by choroidal capillary loss, this study examined the effect of sidestream smoke (SS), the major component of ETS, on the viability of choroidal endothelial cells (EC), with an emphasis on the role of aberrant cell and basement membrane (BM) architecture in mediating SS-induced response. Methods: Chorioretinal ECs (RF/6A) were treated with SS and cell viability and architecture were analyzed by colorimetric assay and actin cytoskeletal organization, respectively. The structure of RF/6A EC-secreted BM was examined by immunofluorescence for collagen IV and immunoblotting for lysyl oxidase (LOX), a collagen-crosslinking enzyme. Finally, fresh RF/6A ECs were cultured on decellularized SS-treated BM to evaluate its active role in EC dysfunction. Results: RF/6A EC viability decreased progressively with increasing SS dose, which correlated strongly with a significant decline in actin cytoskeleton-dependent EC spreading. SS also caused marked disruption of the RF/6A EC-secreted BM that was accompanied by suppression of LOX expression. Further, fresh, non SS-treated RF/6A ECs exhibited a significant loss in viability and actin cytoskeletal organization when cultured on SS-treated corrupt BM. Conclusions: These findings indicate that aberrant physical cues in the form of EC and BM architecture likely play an important role in choriocapillaris dysfunction seen in SS-associated early AMD and implicate choroidal BM as a potential target for AMD management strategies.

PMID: 24713480 [PubMed - as supplied by publisher]

Biochem J. 2014 Apr 9. [Epub ahead of print]

Retinal metabolism in human retina induces the formation of an unprecedented lipofuscin fluorophore "pdA2E"

Wu Y, Jin Q, Yao K, Zhao J, Chen J, Wu X, Gan L, Li J, Song X, Liu X, Cai X.

Abstract: Toxic lipofuscin in the retinal pigment epithelium (RPE)is implicated in blindness in age-related macular degeneration (AMD) or recessive Stargardt disease patients. In this study, we identified a novel fluorescent lipofuscin component in human and bovine RPEs. Using one- and two-dimensional NMR and mass spectrometry, we confirmed the structure of this pigment and called it pdA2E. It exhibits absorbance maxima at 492 and 342 nm and is susceptible to photocatalytic isomerization and oxidation. This fluorophore was also detected in the eyecup extracts of Abca4-/-Rdh8-/-mice, an AMD/recessive Stargardt model. Excess amassing of pdA2E within RPE cells caused significant cell viability loss and membrane

damage. The formation of pdA2E occurred when all-trans-retinal (atRAL) reacted with excess ethanolamine in the absence of acetic acid, and the process likely involves the participation of three atRAL molecules. Our findings suggest that endogenous pdA2E may serve as a sensitizer for yielding singlet oxygen and a singlet oxygen quencher, as well as a side-product of retinal metabolism, and its complete characterization facilitates the understanding of biosynthetic pathwaysby which adverse RPE lipofuscin constituents form.

PMID: 24712709 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2014 Apr 4. pii: S0002-9394(14)00168-8. doi: 10.1016/j.ajo.2014.03.014. [Epub ahead of print]

Immune Responses in Age Related Macular Degeneration and a possible Long Term Therapeutic Strategy for Prevention.

Nussenblatt RB, Lee RW, Chew E, Wei L, Liu B, Sen N, Dick AD, Ferris FL.

PURPOSE: To describe the immune alterations associated with age related macular degeneration (AMD). Based on these findings, to offer an approach to possibly prevent the expression of late disease.

DESIGN: Perspective

METHODS: Review of the existing literature dealing with epidemiology, models, and immunologic findings in patients.

RESULTS: Significant genetic associations have been identified and reported, but environmentally induced (including epigenetic) changes are also an important consideration. Immune alterations include a strong interleukin-17 family signature as well as marked expression of these molecules in the eye. Oxidative stress as well as other homeostatic altering mechanisms occurs throughout life. With this immune dysregulation there is a rationale for considering immunotherapy. Indeed immunotherapy has been shown to affect the late stages of AMD.

CONCLUSION: Immune dysregulation appears to be an underlying alteration in AMD as in other diseases thought to be degenerative and due to aging. Parainflammation and immunosensescence may importantly contribute to the development of disease. The role of complement factor H still needs to be better defined but in light of its association with ocular inflammatory conditions such as sarcoidosis, it does not appear to be unique to AMD but rather may be a marker for retinal pigment epithelium function. With the strong interleukin-17 family signature and the need to treat early on in the disease process, oral tolerance may be considered to prevent disease progression.

PMID: 24709810 [PubMed - as supplied by publisher]

Neurobiol Aging. 2014 Mar 15. pii: S0197-4580(14)00242-5. doi: 10.1016/j.neurobiolaging.2014.03.008. [Epub ahead of print]

Intracellular amyloid beta alters the tight junction of retinal pigment epithelium in 5XFAD mice.

Park SW, Kim JH, Mook-Jung I, Kim KW, Park WJ, Park KH, Kim JH.

Abstract: Extracellular deposit of amyloid beta (Aβ) is a common pathologic feature in both age-related macular degeneration (AMD) and Alzheimer's disease, but the role of intracellular Aβ on the tight junction of the retinal pigment epithelium (RPE) is unknown. In this study, we investigated the intracellular Aβ expression and its role on the outer blood retinal barrier in the retina of 5XFAD mice, a mouse model of Alzheimer's disease. The retina of 5XFAD mice showed the pathologic features of AMD with intracellular Aβ in the RPE. As intracellular Aβ accumulated, zonular occludens-1 and occludin were markedly attenuated and lost their integrity as tight junctions in the RPE of 5XFAD mice. Also, Aβ42 uptake by ARPE

-19 cells induced the tight junction breakdown of zonular occludens-1 and occludin without cell death. These results implicate that intracellular Aβ42 could play a role in the breakdown of the outer blood retinal barrier in 5XFAD mice. Thus, we suggested that 5XFAD mice could be a mouse model of dry AMD with regard to the Aβ42 related pathology.

PMID: 24709310 [PubMed - as supplied by publisher]

Proc Natl Acad Sci U S A. 2014 Apr 1;111(13):5024-9. doi: 10.1073/pnas.1400780111. Epub 2014 Mar 20.

ATP-binding cassette transporter ABCA4 and chemical isomerization protect photoreceptor cells from the toxic accumulation of excess 11-cis-retinal.

Quazi F, Molday RS.

Abstract: The visual cycle is a series of enzyme-catalyzed reactions which converts all-trans-retinal to 11-cis-retinal for the regeneration of visual pigments in rod and cone photoreceptor cells. Although essential for vision, 11-cis-retinal like all-trans-retinal is highly toxic due to its highly reactive aldehyde group and has to be detoxified by either reduction to retinol or sequestration within retinal-binding proteins. Previous studies have focused on the role of the ATP-binding cassette transporter ABCA4 associated with Stargardt macular degeneration and retinol dehydrogenases (RDH) in the clearance of all-trans-retinal from photoreceptors following photoexcitation. How rod and cone cells prevent the accumulation of 11-cis-retinal in photoreceptor disk membranes in excess of what is required for visual pigment regeneration is not known. Here we show that ABCA4 can transport N-11-cis-retinylidene-phosphatidylethanolamine (PE), the Schiff-base conjugate of 11-cis-retinal and PE, from the lumen to the cytoplasmic leaflet of disk membranes. This transport function together with chemical isomerization to its all-trans isomer and reduction to all-trans-retinol by RDH can prevent the accumulation of excess 11-cis-retinal and its Schiff-base conjugate and the formation of toxic bisretinoid compounds as found in ABCA4-deficient mice and individuals with Stargardt macular degeneration. This segment of the visual cycle in which excess 11-cis-retinal is converted to all-trans-retinol provides a rationale for the unusually high content of PE and its long-chain unsaturated docosahexaenoyl group in photoreceptor membranes and adds insight into the molecular mechanisms responsible for Stargardt macular degeneration.

PMID: 24707049 [PubMed - in process]

PLoS One. 2014 Apr 4;9(4):e93343. doi: 10.1371/journal.pone.0093343. eCollection 2014.

Synthesis and propagation of complement c3 by microglia/monocytes in the aging retina.

Rutar M, Valter K, Natoli R, Provis JM.

INTRODUCTION: Complement activation is thought to contribute to the pathogenesis of age-related macular degeneration (AMD), which may be mediated in part by para-inflammatory processes. We aimed to investigate the expression and localization of C3, a crucial component of the complement system, in the retina during the course of aging.

METHODS: SD rats were born and reared in low-light conditions, and euthanized at post-natal (P) days 100, 450, or 750. Expression of C3, IBA1, and Ccl- and Cxcl- chemokines was assessed by qPCR, and in situ hybridization. Thickness of the ONL was assessed in retinal sections as a measure of photoreceptor loss, and counts were made of C3-expressing monocytes.

RESULTS: C3 expression increased significantly at P750, and correlated with thinning of the ONL, at P750, and up-regulation of GFAP. In situ hybridization showed that C3 was expressed by microglia/monocytes, mainly from within the retinal vasculature, and occasionally the ONL. The number of C3-expressing

microglia increased significantly by P750, and coincided spatiotemporally with thinning of the ONL, and up-regulation of Ccl- and Cxcl- chemokines.

CONCLUSIONS: Our data suggest that recruited microglia/monocytes contribute to activation of complement in the aging retina, through local expression of C3 mRNA. C3 expression coincides with age-related thinning of the ONL at P750, although it is unclear whether the C3-expressing monocytes are a cause or consequence. These findings provide evidence of activation of complement during natural aging, and may have relevance to cellular events underling the pathogenesis of age-related retinal diseases.

PMID: 24705166 [PubMed - in process] PMCID: PMC3976274

Proc Natl Acad Sci U S A. 2014 Apr 8;111(14):E1428-37. doi: 10.1073/pnas.1317986111. Epub 2014 Mar 24.

Two-photon microscopy reveals early rod photoreceptor cell damage in light-exposed mutant mice.

Maeda A, Palczewska G, Golczak M, Kohno H, Dong Z, Maeda T, Palczewski K.

Abstract: Atrophic age-related and juvenile macular degeneration are especially devastating due to lack of an effective cure. Two retinal cell types, photoreceptor cells and the adjacent retinal pigmented epithelium (RPE), reportedly display the earliest pathological changes. Abca4(-/-)Rdh8(-/-) mice, which mimic many features of human retinal degeneration, allowed us to determine the sequence of light-induced events leading to retinal degeneration. Using two-photon microscopy with 3D reconstruction methodology, we observed an initial strong retinoid-derived fluorescence and expansion of Abca4(-/-)Rdh8(-/-) mouse rod cell outer segments accompanied by macrophage infiltration after brief exposure of the retina to bright light. Additionally, light-dependent fluorescent compounds produced in rod outer segments were not transferred to the RPE of mice genetically defective in RPE phagocytosis. Collectively, these findings suggest that for light-induced retinopathies in mice, rod photoreceptors are the primary site of toxic retinoid accumulation and degeneration, followed by secondary changes in the RPE.

PMID: 24706832 [PubMed - in process]

Proc Natl Acad Sci U S A. 2014 Apr 8;111(14):E1402-8. doi: 10.1073/pnas.1400530111. Epub 2014 Mar 24.

Beta cyclodextrins bind, stabilize, and remove lipofuscin bisretinoids from retinal pigment epithelium.

Nociari MM, Lehmann GL, Perez Bay AE, Radu RA, Jiang Z, Goicochea S, Schreiner R, Warren JD, Shan J, Adam de Beaumais S, Ménand M, Sollogoub M, Maxfield FR, Rodriguez-Boulan E.

Abstract: Accumulation of lipofuscin bisretinoids (LBs) in the retinal pigment epithelium (RPE) is the alleged cause of retinal degeneration in genetic blinding diseases (e.g., Stargardt) and a possible etiological agent for age-related macular degeneration. Currently, there are no approved treatments for these diseases; hence, agents that efficiently remove LBs from RPE would be valuable therapeutic candidates. Here, we show that beta cyclodextrins (β-CDs) bind LBs and protect them against oxidation. Computer modeling and biochemical data are consistent with the encapsulation of the retinoid arms of LBs within the hydrophobic cavity of β-CD. Importantly, β-CD treatment reduced by 73% and 48% the LB content of RPE cell cultures and of eyecups obtained from Abca4-Rdh8 double knock-out (DKO) mice, respectively. Furthermore, intravitreal administration of β-CDs reduced significantly the content of bisretinoids in the RPE of DKO animals. Thus, our results demonstrate the effectiveness of β-CDs to complex and remove LB deposits from RPE cells and provide crucial data to develop novel prophylactic approaches for retinal disorders elicited by LBs.

PMID: 24706818 [PubMed - in process]

Genetics

C R Biol. 2014 Mar;337(3):178-84. doi: 10.1016/j.crvi.2013.12.003. Epub 2014 Feb 25.

Complement factor H and related proteins in age-related macular degeneration.

Calippe B, Guillonneau X, Sennlaub F.

Abstract: Age-related macular degeneration (AMD) is the major cause of legal blindness in the industrialized world. Polymorphisms and recently discovered rare mutations of the Complement Factor H gene have been shown to be strongly associated with AMD. The deletion of CFH-related proteins 1 and 3, proteins that share homologous regions with CFH, is found in protective haplotypes. The following is a critical review of the current state of knowledge of the implication of CFH and CFH-related proteins 1 and 3 in AMD.

PMID: 24702844 [PubMed - in process]

BMC Bioinformatics. 2014 Apr 10;15(1):102. [Epub ahead of print]

Cloud computing for detecting high-order genome-wide epistatic interaction via dynamic clustering.

Guo X, Meng Y, Yu N, Pan Y.

Backgroud: Taking the advantage of high-throughput single nucleotide polymorphism (SNP) genotyping technology, large genome-wide association studies (GWASs) have been considered to hold promise for unravelling complex relationships between genotype and phenotype. At present, traditional single-locus-based methods are insufficient to detect interactions consisting of multiple-locus, which are broadly existing in complex traits. In addition, statistic tests for high order epistatic interactions with more than 2 SNPs propose computational and analytical challenges because the computation increases exponentially as the cardinality of SNPs combinations gets larger.

RESULTS: In this paper, we provide a simple, fast and powerful method using dynamic clustering and cloud computing to detect genome-wide multi-locus epistatic interactions. We have constructed systematic experiments to compare powers performance against some recently proposed algorithms, including TEAM, SNPRuler, EDCF and BOOST. Furthermore, we have applied our method on two real GWAS datasets, Age -related macular degeneration (AMD) and Rheumatoid arthritis (RA) datasets, where we find some novel potential disease-related genetic factors which are not shown up in detections of 2-loci epistatic interactions.

CONCLUSIONS: Experimental results on simulated data demonstrate that our method is more powerful than some recently proposed methods on both two- and three-locus disease models. Our method has discovered many novel high-order associations that are significantly enriched in cases from two real GWAS datasets. Moreover, the running time of the cloud implementation for our method on AMD dataset and RA dataset are roughly 2 hours and 50 hours on a cluster with forty small virtual machines for detecting two-locus interactions, respectively. Therefore, we believe that our method is suitable and effective for the full-scale analysis of multiple-locus epistatic interactions in GWAS.

PMID: 24717145 [PubMed - as supplied by publisher]

Diet & lifestyle

J Biol Chem. 2014 Apr 7. [Epub ahead of print]

Smoke-exposure causes endoplasmic reticulum stress and lipid accumulation in retinal pigment

epithelium through oxidative stress and complement activation.

Kunchithapautham K1, Atkinson C, Rohrer B.

Abstract: Age-related macular degeneration is a complex disease caused by genetic and environmental factors, including genetic variants in complement components and smoking. Smoke exposure leads to oxidative stress, complement activation, endoplasmic reticulum (ER) stress, and lipid dysregulation, which have all been proposed to be associated with AMD pathogenesis. Here we examine the effects of smoke exposure on the retinal pigment epithelium (RPE). Mice were exposed to cigarette smoke or filtered air for 6 months. RPE cells grown as stable monolayers were exposed to 5% cigarette smoke extract (CSE). Effects of smoke were determined by biochemical, molecular and histological measures. Effects of the alternative pathway (AP) of complement and complement C3a anaphylatoxin receptor signaling were analyzed using knockout mice or specific inhibitors. ER stress markers were elevated after smoke exposure in RPE of intact mice, which was eliminated in AP-deficient mice. To examine this relationship further, RPE monolayers were exposed to CSE. Short-term smoke exposure resulted in production and release of complement C3, the generation of C3a, oxidative stress, complement activation on the cell membrane, and ER stress. Long-term exposure to CSE resulted in lipid accumulation, and secretion. All measures were reversed by blocking C3a complement receptor (C3aR), alternative complement pathway signaling, and anti-oxidant therapy. Taken together, our results provide clear evidence that smoke exposure results in oxidative stress and complement activation via the AP, resulting in ER stress-mediated lipid accumulation, and further suggesting that oxidative stress and complement act synergistically in the pathogenesis of AMD.

PMID: 24711457 [PubMed - as supplied by publisher]

Biomed Res Int. 2014;2014:768026. Epub 2014 Feb 23.

Oxidative Stress, Hypoxia, and Autophagy in the Neovascular Processes of Age-Related Macular Degeneration.

Blasiak J, Petrovski G, Veréb Z, Facskó A, Kaarniranta K.

Abstract: Age-related macular degeneration (AMD) is the leading cause of severe and irreversible loss of vision in the elderly in developed countries. AMD is a complex chronic neurodegenerative disease associated with many environmental, lifestyle, and genetic factors. Oxidative stress and the production of reactive oxygen species (ROS) seem to play a pivotal role in AMD pathogenesis. It is known that the macula receives the highest blood flow of any tissue in the body when related to size, and anything that can reduce the rich blood supply can cause hypoxia, malfunction, or disease. Oxidative stress can affect both the lipid rich retinal outer segment structure and the light processing in the macula. The response to oxidative stress involves several cellular defense reactions, for example, increases in antioxidant production and proteolysis of damaged proteins. The imbalance between production of damaged cellular components and degradation leads to the accumulation of detrimental products, for example, intracellular lipofuscin and extracellular drusen. Autophagy is a central lysosomal clearance system that may play an important role in AMD development. There are many anatomical changes in retinal pigment epithelium (RPE), Bruch's membrane, and choriocapillaris in response to chronic oxidative stress, hypoxia, and disturbed autophagy and these are estimated to be crucial components in the pathology of neovascular processes in AMD.

PMID: 24707498 [PubMed - as supplied by publisher] PMCID: PMC3950832

Prog Retin Eye Res. 2014 Apr 3. pii: S1350-9462(14)00015-9. doi: 10.1016/j.preteyeres.2014.03.002. [Epub ahead of print]

Cholesterol in the retina: the best is yet to come.

Pikuleva IA, Curcio CA.

Abstract: Historically understudied, cholesterol in the retina is receiving more attention now because of genetic studies showing that several cholesterol-related genes are risk factors for age-related macular degeneration (AMD) and because eye pathology studies showing high cholesterol content of drusen, aging Bruch's membrane, and newly found subretinal lesions. The challenge before us is determining how the cholesterol-AMD link is realized. Meeting this challenge will require an excellent understanding these genes' roles in retinal physiology and how chorioretinal cholesterol is maintained. In the first half of this review, we will succinctly summarize physico-chemical properties of cholesterol, its distribution in the human body, general principles of maintenance and metabolism, and differences in cholesterol handling in human and mouse that impact on experimental approaches. This information will provide a backdrop to the second part of the review focusing on unique aspects of chorioretinal cholesterol homeostasis, aging in Bruch's membrane, cholesterol in AMD lesions, a model for lesion biogenesis, a model for macular vulnerability based on vascular biology, and alignment of AMD-related genes and pathobiology using cholesterol and an atherosclerosis-like progression as unifying features. We conclude with recommendations for the most important research steps we can take towards delineating the cholesterol-AMD link.

PMID: 24704580 [PubMed - as supplied by publisher]