

Issue 28

Monday May 16, 2011

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".

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

Retina. 2011 May 6. [Epub ahead of print]

INTRAVITREAL BEVACIZUMAB VERSUS COMBINED INTRAVITREAL BEVACIZUMAB AND TRIAMCINOLONE FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: Six-Month Results of a Randomized Clinical Trial.

Ahmadi H, Taei R, Riazi-Esfahani M, Piri N, Homayouni M, Daftarian N, Yaseri M.

From the *Ophthalmic Research Center, Labbafinejad Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran; and †Eye Research Center, Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran.

PURPOSE: To determine whether combined intravitreal bevacizumab (IVB) and triamcinolone (IVT) is more effective than IVB alone in neovascular age-related macular degeneration.

METHODS: This was a prospective, randomized clinical trial performed at two centers. Eligible eyes were assigned randomly to one of the two study arms. In the IVB group, 3 consecutive injections of 1.25 mg of bevacizumab were given 6 weeks apart, while in the IVB/IVT group, the first of the triple IVB injections was combined with 2 mg of IVB. A fourth IVB was injected in eyes demonstrating active choroidal neovascularization at Week 24.

RESULTS: Sixty and 55 eyes were in the IVB and IVB/IVT groups, respectively. Best-corrected visual acuity improved, and central macular thickness was reduced significantly in both groups at all time points. Visual improvement was more pronounced in the IVB/IVT group compared with the IVB group 6 weeks (8.5 ± 14.4 vs. 3.8 ± 8.9 letters, $P = 0.04$) and 12 weeks (11.8 ± 16.6 vs. 6.2 ± 10.8 letters, $P = 0.03$) after initiation of therapy. However, there was no significant difference in visual improvement at Week 24 (11.3 ± 17.2 letters in the IVB/IVT group vs. 8.7 ± 15.6 letters in the IVB group, $P = 0.40$). The IVB/IVT group showed significantly less need for a fourth injection at Week 24 (34.5% vs. 53.3% in the IVB/IVT and IVB groups, respectively, $P = 0.04$).

CONCLUSION: Mandated therapy with IVB improved best-corrected visual acuity and decreased central macular thickness in neovascular age-related macular degeneration. The addition of low-dose IVT temporarily increased the therapeutic efficacy in the early postinjection period and resulted in fewer requirements for repeat IVB injections at 6 months; however, final levels of visual improvement were comparable in the 2 study groups.

PMID: 21555967 [PubMed - as supplied by publisher]

Singapore Med J. 2011 Apr;52(4):232-40.

Optimising the management of choroidal neovascularisation in Asian patients: consensus on treatment recommendations for anti-VEGF therapy.

Koh A, Lim TH, Au Eong KG, Chee C, Ong SG, Tan N, Yeo I, Wong D.

Eye and Retina Surgeons, Camden Medical Centre, 1 Orchard Boulevard, Singapore 248649. ah-ckoh@yahoo.com.

Abstract

In Asian countries, age-related macular degeneration (AMD), specifically wet AMD or choroidal neovascularisation (CNV), is an important cause of blindness and visual handicap. Vascular endothelial growth factors (VEGF) play an integral role in the development of CNV and thus provide an important therapeutic target. Current treatment paradigms for neovascular AMD recognise the place of photodynamic therapy (PDT) in the management of this condition. However, combination therapy targeting different pathways to produce a synergistic effect may result in improved visual outcomes and reduced duration of treatment. Anti-VEGF therapy has greatly improved treatment outcomes in patients with CNV, and a growing body of evidence supports the role of these agents as monotherapy or in combination with PDT. In particular, anti-VEGF may be a first-line treatment option in certain types of subfoveal myopic CNV as well as for classic and occult juxtafoveal and subfoveal CNV. The implementation of evidence-based medicine into current clinical practice is paramount to improving patient care. The authors, who are also members of the Singapore Medical Retina Advisory Board, outline the consensus points and recommended treatment algorithms based on currently available knowledge to provide a structured management approach to the treatment of Asian patients with CNV.

PMID: 21552782 [PubMed - in process]

J Fr Ophtalmol. 2011 May 6. [Epub ahead of print]

[Efficacy of three intravitreal injections of bevacizumab in the treatment of exudative age-related macular degeneration.]

[Article in French]

Bidot ML, Malvitte L, Bidot S, Bron A, Creuzot-Garcher C.

Service d'ophtalmologie, CHU de Dijon, 32, rue du Faubourg-Raines, BP 1519, 21033 Dijon cedex, France.

INTRODUCTION: To evaluate intravitreal bevacizumab therapy for choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).

MATERIAL AND METHODS: A retrospective review between June 2006 and May 2008 of patients with CNV secondary to AMD was conducted. All patients were treated with intravitreal injection of bevacizumab (1.25mg) once a month during a 3-month-period. The mean evaluation criteria were the best-corrected visual acuity (BCVA) logMar testing before and one month after the third injection. All eyes underwent an angiography and an optical coherence tomography before injections to define the activity and the type of CNV and then to evaluate the persistence of leakage (macular edema, subretinal fluid, and pigment epithelial detachment) after treatment. Then treatments were left to the investigator's discretion during the following six months.

RESULTS: Seventy-one eyes of 66 patients were enrolled. There were 65% occult CNV, 20% classic CNV, and 15% combined. A significant improvement in BCVA was observed, from 0.88 ± 0.57 to 0.77 ± 0.60 ($p=0.001$), one month after the third injection. At this time, 57.7% of the eyes required a reinjection because of leakage persistence. A concomitant treatment with intravitreal triamcinolone injection and/or photody-

namic therapy was necessary for 8% of nonresponder eyes. Six months after initial treatment, a complete resolution of exudative signs was not obtained for 33.8% of eyes. The average number of injections was 3.85 ± 0.96 during the 9-month follow-up. BCVA stability was observed at 4, 6 and 9-month follow-ups ($F(71.2)=1.54$; $p=0.46$). Three complications occurred: one endophthalmitis, one retinal tear, and one vitreous hemorrhage secondary to a macular hemorrhage.

DISCUSSION: Mean BCVA significantly improved at one month after three consecutive monthly intravitreal injections of bevacizumab. However, most eyes required a reinjection.

CONCLUSION: In spite of improvement in BCVA, leakage of the CNV persisted in most eyes after three monthly intravitreal injections of bevacizumab. Then retreatment and sometimes concomitant treatment was necessary to obtain complete resolution of exudative signs and BCVA stability.

PMID: 21550687 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Br J Ophthalmol. 2011 May 7. [Epub ahead of print]

Incidence and regression of Charles Bonnet syndrome in vascular age-related macular degeneration.

Meyer CH, Fleckenstein M, Rodrigues EB, Mennel S.

University of Bonn, Bonn, Germany.

PMID: 21551463 [PubMed - as supplied by publisher]

Arch Ophthalmol. 2011 May;129(5):575-9.

Retinal pigment epithelium tears secondary to age-related macular degeneration: a simultaneous confocal scanning laser ophthalmoscopy and spectral-domain optical coherence tomography study.

Caramoy A, Kirchhof B, Fauser S.

Center of Ophthalmology, Department of Vitreoretinal Surgery, University of Cologne, Kerpenerstr 62, 50924 Cologne, Germany. acaramoy@yahoo.co.uk.

OBJECTIVE: To describe the morphology of retinal pigment epithelium (RPE) tears secondary to age-related macular degeneration by using high-resolution, spectral-domain optical coherence tomography (SD-OCT).

METHODS: For simultaneous topographic and tomographic in vivo imaging, confocal scanning laser ophthalmoscopy and spectral-domain optical coherence tomography were applied in combination. Retina over the RPE-denuded area was particularly examined for signs of viable photoreceptors.

RESULTS: A total of 26 patients (28 eyes) were included in the study. The mean (SD) age of patients was 78 (8) years (age range, 62-91 years). In cases with recent RPE tears, external limiting membrane, photoreceptor inner and outer segment junction, and nonatrophic outer nuclear layer could be identified in the retina on the RPE-denuded area. Intact external limiting membrane, photoreceptor inner and outer segment junction, and nonatrophic outer nuclear layer could be seen in 1 patient for up to 325 days after the RPE tear. In fibrotic older RPE tears, these structures were atrophic.

CONCLUSIONS: In this study, signs for viable photoreceptors could be identified for up to 325 days after

an RPE tear using spectral-domain optical coherence tomography. This finding is important to consider in future therapies aimed at rescuing photoreceptors after RPE tears.

PMID: 21555609 [PubMed - in process]

Arch Ophthalmol. 2011 May;129(5):580-4.

Pattern electroretinography in age-related macular degeneration.

Sheybani A, Brantley MA Jr, Apte RS.

Department of Ophthalmology and Visual Sciences, School of Medicine, Washington University in St Louis, 660 S Euclid Ave, PO Box 8096, St Louis, MO 63110. apte@vision.wustl.edu.

OBJECTIVE: To determine whether prolonged vascular endothelial growth factor inhibition is toxic to the retina by using pattern electroretinographic imaging in participants with neovascular age-related macular degeneration (AMD).

METHODS: We performed a prospective, single-arm clinical trial of 17 eyes in 17 treatment-naïve participants with subfoveal choroidal neovascularization from AMD. On-label intravitreal ranibizumab was injected monthly for 6 months. Then pattern electroretinographic imaging was performed before and at 1 month, 3 months, and 6 months after first treatment, and results were interpreted by a trained reader masked to the clinical data. The primary outcome measure was the change in pattern electroretinographic imaging (positive wave peaking at 50 milliseconds [P50] and negative wave peaking at 95 milliseconds [N95] values) from baseline at 6 months. The secondary outcome measure was the change in visual acuity at 6 months.

RESULTS: The mean participant age was 79.6 years (range, 69.5-90.4 years). At baseline, mean (SD) P50 and N95 amplitudes were 1.3 (0.69) μ V and 1.5 (0.71) μ V, respectively. By 6 months, no decrease in P50 or N95 amplitudes from baseline was observed (1.4 [0.47] μ V, $P = .46$; and 1.8 [0.96] μ V, $P = .14$, respectively). Mean visual acuity before treatment was 20/85 with improvement to a mean of 20/55 ($P = .004$) at 6 months.

CONCLUSIONS: This study found no decrease in P50 and N95 amplitudes in participants treated with ranibizumab for neovascular AMD. These findings indicate that vascular endothelial growth factor inhibition with monthly injections of ranibizumab for 6 months likely does not lead to retinal damage. Trial Registration clinicaltrials.gov Identifier: NCT00500344.

PMID: 21555610 [PubMed - in process]

Arch Ophthalmol. 2011 May;129(5):628-32.

Pilot study of the delivery of microcollimated pars plana external beam radiation in porcine eyes.

Barakat MR, Shusterman M, Moshfeghi D, Danis R, Gertner M, Singh RP.

9500 Euclid Ave, i-32, Cleveland, OH 44195. singhr@ccf.org.

OBJECTIVE: To investigate the effects of a novel stereotactic radiosurgical system for pars plana delivery of microcollimated x-rays to the retina and determine the retinal radiological dose response and toxicity threshold in a pig model.

METHODS: The x-rays were delivered through the pars plana to the maculae of Yucatan miniswine to verify the targeting and safety of a cornea-scleral, stabilized, office-based delivery system. Twelve eyes were randomized to receive 0, 16, 24, 42, 60, or 90 Gy in a single dose to the retina. Eye examinations, fundus

photography, fluorescein angiography, and spectral-domain optical coherence tomography were obtained at days 7, 30, 60, and 90. Indocyanine green angiography was done at day 90.

RESULTS: Through day 90 interim analysis, no abnormalities of external structures were noted. A small cortical lens opacity was noted in the 60-Gy group. Fundus evaluation revealed no abnormalities at 16 or 24 Gy. Beginning at day 30, circular pale retinal lesions with sharp margins were noted in the maculae of the eyes that received 42, 60, and 90 Gy. Higher-dose lesions showed late staining on fluorescein angiography, choroidal hypoperfusion on indocyanine green angiography, and defined photoreceptor loss and retinal thinning on spectral-domain optical coherence tomography.

CONCLUSION: Transscleral stereotactic radiation dosing of porcine eyes demonstrates no apparent clinical abnormalities in doses less than 24 Gy. Doses of 42 Gy or higher led to focal choroidal and retinal damage within the target area. **Clinical Relevance** Radiation can induce small-blood vessel closure and thereby has therapeutic potential in neovascular diseases such as age-related macular degeneration.

PMID: 21555617 [PubMed - in process]

J Fr Ophtalmol. 2011 May 6. [Epub ahead of print]

Perifoveal exudative vascular anomalous complex.

Querques G, Kuhn D, Massamba N, Leveziel N, Querques L, Souied EH.

Service d'ophtalmologie, centre hospitalier intercommunal de Créteil, université de Paris-XII, 40, avenue de Verdun, 94000 Créteil, France.

PURPOSE: To report the angiographic and optical coherence tomography (OCT) features of isolated "perifoveal exudative vascular anomalous complex (PEVAC)", a peculiar clinical entity.

METHODS: A complete ophthalmologic examination was performed in two patients (a 82-year old woman [case 1]; a 52-year old man [case 2]) that were referred to our department for unilateral blurred vision.

RESULTS: In both cases, fundus examination of the right eye showed a perifoveal isolated large aneurismal change, accompanied by small hemorrhages, intraretinal exudation, and small hard exudates accumulation. Both FA and ICGA revealed the absence of any other retinal or choroidal vascular abnormality associated. OCT showed a round hyperreflective lesion in correspondence of the perifoveal vascular anomalous complex, surrounded by intraretinal cystic spaces. In case 2, the lesion remained unchanged despite 3 monthly intravitreal injections of ranibizumab.

CONCLUSION: PEVAC may develop in absence of capillary ischemia or inflammation, probably due to progressive retinal endothelial cell degeneration. This could explain the unresponsiveness to anti-VEGF treatments.

PMID: 21550688 [PubMed - as supplied by publisher]

Epidemiology & pathogenesis

PLoS One. 2011 Apr 28;6(4):e19078.

A Non Membrane-Targeted Human Soluble CD59 Attenuates Choroidal Neovascularization in a Model of Age Related Macular Degeneration.

Cashman SM, Ramo K, Kumar-Singh R.

Department of Ophthalmology, Tufts University School of Medicine, Boston, Massachusetts, United States

of America.

Abstract

Age related macular degeneration (AMD) is the most common cause of blindness amongst the elderly. Approximately 10% of AMD patients suffer from an advanced form of AMD characterized by choroidal neovascularization (CNV). Recent evidence implicates a significant role for complement in the pathogenesis of AMD. Activation of complement terminates in the incorporation of the membrane attack complex (MAC) in biological membranes and subsequent cell lysis. Elevated levels of MAC have been documented on choroidal blood vessels and retinal pigment epithelium (RPE) of AMD patients. CD59 is a naturally occurring membrane bound inhibitor of MAC formation. Previously we have shown that membrane bound human CD59 delivered to the RPE cells of mice via an adenovirus vector can protect those cells from human complement mediated lysis *ex vivo*. However, application of those observations to choroidal blood vessels are limited because protection from MAC-mediated lysis was restricted only to the cells originally transduced by the vector. Here we demonstrate that subretinal delivery of an adenovirus vector expressing a transgene for a soluble non-membrane binding form of human CD59 can attenuate the formation of laser-induced choroidal neovascularization and murine MAC formation in mice even when the region of vector delivery is distal to the site of laser induced CNV. Furthermore, this same recombinant transgene delivered to the intravitreal space of mice by an adeno-associated virus vector (AAV) can also attenuate laser-induced CNV. To our knowledge, this is the first demonstration of a non-membrane targeting CD59 having biological potency in any animal model of disease *in vivo*. We propose that the above approaches warrant further exploration as potential approaches for alleviating complement mediated damage to ocular tissues in AMD.

PMID: 21552568 [PubMed - in process]

PMCID: PMC3084256

Proc Natl Acad Sci U S A. 2011 May 9. [Epub ahead of print]

Common polymorphisms in C3, factor B, and factor H collaborate to determine systemic complement activity and disease risk.

Heurich M, Martínez-Barricarte R, Francis NJ, Roberts DL, Rodríguez de Córdoba S, Morgan BP, Harris CL.

Department of Infection, Immunity and Biochemistry, School of Medicine, Cardiff University, Cardiff CF14 4XN, United Kingdom.

Abstract

Common polymorphisms in complement alternative pathway (AP) proteins C3 (C3(R102G)), factor B (fB(R32Q)), and factor H (fH(V62I)) are associated with age-related macular degeneration (AMD) and other pathologies. Our published work showed that fB(R32Q) influences C3 convertase formation, whereas fH(V62I) affects factor I cofactor activity. Here we show how C3(R102G) (C3S/F) influences AP activity. In hemolysis assays, C3(102G) activated AP more efficiently (EC(50) C3(102G): 157 nM; C3(102R): 191 nM; $P < 0.0001$). fB binding kinetics and convertase stability were identical, but native and recombinant fH bound more strongly to C3b(102R) (K(D) C3b(102R): 1.0 μ M; C3b(102G): 1.4 μ M; $P < 0.0001$). Accelerated decay was unaltered, but fH cofactor activity was reduced for C3b(102G), favoring AP amplification. Combining disease "risk" variants (C3(102G), fB(32R), and fH(62V)) in add-back assays yielded sixfold higher hemolytic activity compared with "protective" variants (C3(102R), fB(32Q), and fH(62I); $P < 0.0001$). These data introduce the concept of a functional complotype (combination of polymorphisms) defining complement activity in an individual, thereby influencing susceptibility to AP-driven disease.

PMID: 21555552 [PubMed - as supplied by publisher]

Ophthalmology. 2011 May 5. [Epub ahead of print]

A Prospective Study of Reticular Macular Disease.

Pumariega NM, Smith RT, Sohrab MA, Letien V, Souied EH.

Department of Ophthalmology, Harkness Eye Institute, Columbia University, New York, New York.

PURPOSE: To determine the risk of progression to advanced age-related macular degeneration (AMD) conferred by reticular pseudodrusen (RPD), an imaging presentation of reticular macular disease (RMD), in high-risk fellow eyes of subjects with AMD and unilateral choroidal neovascularization (CNV) in a large, prospective study.

DESIGN: Cohort study.

PARTICIPANTS: Two hundred seventy-one subjects with AMD; 94 with RPD and 177 without RPD.

METHODS: Images from a cohort of 271 subjects with AMD in the Nutritional AMD treatment phase II (NAT 2) Study, a 3-year prospective study of subjects with unilateral CNV and large soft drusen in the fellow eye, were studied. The fellow eye, at high risk for advanced AMD developing, was the study eye. There were 5 visits per subject. Imaging at each visit consisted of color, red-free, and blue-light photography and fluorescein angiography. The images were analyzed for the presence of RPD, following disease progression throughout the 3-year study.

MAIN OUTCOME MEASURES: The development of advanced AMD (CNV or geographic atrophy).

RESULTS: For the 271 subjects who completed the full 3-year study, there was a significantly higher rate of advanced AMD (56% or 53/94) in fellow eyes with RPD at any visit compared with eyes without RPD (32% or 56/177; $P < 0.0001$, chi-square test; relative risk [RR], 1.8; 95% confidence interval [CI], 1.4-2.4). The chance of developing advanced AMD in the fellow eye in women with RPD (66%) was more than double that of women without RPD (30%; $P < 0.00001$; RR, 2.2; 95% CI, 1.6-3.1).

PMID: 21550118 [PubMed - as supplied by publisher]

Genetics

Br J Ophthalmol. 2011 May 10. [Epub ahead of print]

CFH, VEGF and HTRA1 promoter genotype may influence the response to intravitreal ranibizumab therapy for neovascular age-related macular degeneration.

McKibbin M, Ali M, Bansal S, Baxter PD, West K, Williams G, Cassidy F, Inglehearn CF.

St. James's University Hospital, Leeds, UK.

Aims: To investigate an association between genotype for three single nucleotide polymorphisms strongly associated with the development of age-related macular degeneration (AMD) and the early response to treatment with intravitreal ranibizumab for neovascular AMD.

Methods: Best corrected visual acuity letter score was recorded at baseline and each subsequent visit. Age, sex, smoking history, lesion type and the number of injections were also recorded. Genotypes were obtained for rs11200638 in HTRA1, rs1061170 in CFH and rs1413711 in VEGF. Data were analysed with treatment response at month 6 as both a binary (>5 letter improvement vs ≤5 letter gain) and a linear trait.

Results: This initial study cohort consisted of 104 Caucasian neovascular AMD patients treated with intravitreal ranibizumab. Trends towards a more favourable outcome were seen with the higher AMD risk genotypes in CFH and VEGF in both the linear and binary models and in HTRA1 in the linear model alone. For CFH, mean letter score change after 6 months was +1.6, +5.9 and +7.2 letters for the TT, TC and CC genotypes and a >5 letter gain was seen in 34.6%, 56.6% and 56%, respectively. For VEGF, mean letter

score change after 6 months was +1.3, +5.8 and +7.4 letters for the TT, TC and CC genotypes and a >5 letter gain was seen in 40%, 55.8% and 51.9%, respectively. For HTRA1, mean letter score change was +2.2, +7.5 and +2.9 letters for the GG, GA and AA genotypes.

Conclusions: This study reports preliminary evidence suggesting that the higher AMD risk genotypes in CFH, VEGF and HTRA1 may influence the short-term response to treatment with ranibizumab for neovascular AMD.

PMID: 21558292 [PubMed - as supplied by publisher]

Pre-clinical

Age (Dordr). 2011 May 11. [Epub ahead of print]

Neurodegeneration of the retina in mouse models of Alzheimer's disease: what can we learn from the retina?

Chiu K, Chan TF, Wu A, Leung IY, So KF, Chang RC.

Laboratory of Neurodegenerative Diseases, Department of Anatomy, The University of Hong Kong, Pokfulam, Hong Kong, China.

Abstract

Alzheimer's disease (AD) is an age-related progressive neurodegenerative disease commonly found among elderly. In addition to cognitive and behavioral deficits, vision abnormalities are prevalent in AD patients. Recent studies investigating retinal changes in AD double-transgenic mice have shown altered processing of amyloid precursor protein and accumulation of β -amyloid peptides in neurons of retinal ganglion cell layer (RGCL) and inner nuclear layer (INL). Apoptotic cells were also detected in the RGCL. Thus, the pathophysiological changes of retinas in AD patients are possibly resembled by AD transgenic models. The retina is a simple model of the brain in the sense that some pathological changes and therapeutic strategies from the retina may be observed or applicable to the brain. Furthermore, it is also possible to advance our understanding of pathological mechanisms in other retinal degenerative diseases. Therefore, studying AD-related retinal degeneration is a promising way for the investigation on (1) AD pathologies and therapies that would eventually benefit the brain and (2) cellular mechanisms in other retinal degenerations such as glaucoma and age-related macular degeneration. This review will highlight the efforts on retinal degenerative research using AD transgenic mouse models.

PMID: 21559868 [PubMed - as supplied by publisher]

J Biol Chem. 2011 May 12. [Epub ahead of print]

Sublytic membrane-attack-complex (MAC) activation alters regulated rather than constitutive VEGF secretion in retinal pigment epithelium monolayers.

Kunchithapautham K, Rohrer B.

Medical University of South Carolina, United States.

Abstract

Uncontrolled activation of the alternative complement pathway and secretion of vascular endothelial growth factor (VEGF) are thought to be associated with age-related macular degeneration (AMD). Previously, we have shown that in RPE monolayers, oxidative-stress reduced complement inhibition on the cell surface. The resulting increased level of sublytic complement activation resulted in VEGF release, which disrupted the barrier facility of these cells as determined by transepithelial resistance (TER) measurements. Induced rather than basal VEGF release in RPE is thought to be controlled by different mechanisms, including

voltage-dependent calcium channel (VDCC) activation and mitogen-activated protein kinases. Here we examined the potential intracellular links between sublytic complement activation and VEGF release in RPE cells challenged with H₂O₂ and complement-sufficient normal human serum (NHS). Disruption of barrier function by H₂O₂ + NHS rapidly increased Ras expression and Erk and Src phosphorylation, but had no effect on p38 phosphorylation. Either treatment alone had little effect. TER reduction could be attenuated by inhibiting Ras, Erk and Src activation, or blocking VDCC or VEGF-R2 activation, but not by inhibiting p38. Combinatorial analysis of inhibitor effects demonstrated that sublytic complement activation triggers VEGF secretion via two pathways, Src and Ras-Erk, with the latter being amplified by VEGF-R2 activation, but has no effect on constitutive VEGF secretion mediated via p38. Finally, effects on TER were directly correlated with release of VEGF; and sublytic MAC activation decreased levels of zfp36, a negative modulator of VEGF transcription, resulting in increased VEGF expression. Taken together, identifying how sublytic MAC induces VEGF expression and secretion might offer opportunities to selectively inhibit pathological VEGF release only.

PMID: 21566137 [PubMed - as supplied by publisher]

PLoS One. 2011 Apr 29;6(4):e19456.

Age-Related Retinopathy in NRF2-Deficient Mice.

Zhao Z, Chen Y, Wang J, Sternberg P, Freeman ML, Grossniklaus HE, Cai J.

Vanderbilt Eye Institute, Vanderbilt University Medical Center, Nashville, Tennessee, United States of America.

BACKGROUND:

Cumulative oxidative damage is implicated in the pathogenesis of age-related macular degeneration (AMD). Nuclear factor erythroid 2-related factor 2 (NRF2) is a transcription factor that plays key roles in retinal antioxidant and detoxification responses. The purposes of this study were to determine whether NRF2-deficient mice would develop AMD-like retinal pathology with aging and to explore the underlying mechanisms.

METHODS AND FINDINGS:

Eyes of both wild type and Nrf2(-/-) mice were examined in vivo by fundus photography and electroretinography (ERG). Structural changes of the outer retina in aged animals were examined by light and electron microscopy, and immunofluorescence labeling. Our results showed that Nrf2(-/-) mice developed age-dependent degenerative pathology in the retinal pigment epithelium (RPE). Drusen-like deposits, accumulation of lipofuscin, spontaneous choroidal neovascularization (CNV) and sub-RPE deposition of inflammatory proteins were present in Nrf2(-/-) mice after 12 months. Accumulation of autophagy-related vacuoles and multivesicular bodies was identified by electron microscopy both within the RPE and in Bruch's membrane of aged Nrf2(-/-) mice.

CONCLUSIONS:

Our data suggest that disruption of Nfe2l2 gene increased the vulnerability of outer retina to age-related degeneration. NRF2-deficient mice developed ocular pathology similar to cardinal features of human AMD and deregulated autophagy is likely a mechanistic link between oxidative injury and inflammation. The Nrf2(-/-) mice can provide a novel model for mechanistic and translational research on AMD.

PMID: 21559389 [PubMed - in process]

Disclaimer: This newsletter is provided as a free service to eye care professionals by the Macular Degeneration Foundation. The Macular Degeneration Foundation cannot be liable for any error or omission in this publication and makes no warranty of any kind, either expressed or implied in relation to this publication.