

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.

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Drug treatment

Br J Ophthalmol. 2014 Sep 5. pii: bjophthalmol-2014-305327. doi: 10.1136/bjophthalmol-2014-305327. [Epub ahead of print]

Multi-country real-life experience of anti-vascular endothelial growth factor therapy for wet age-related macular degeneration.

Holz FG, Tadayoni R, Beatty S, Berger A, Cereda MG, Cortez R, Hoyng CB, Hykin P, Staurenghi G, Heldner S, Bogumil T, Heah T, Sivaprasad S.

BACKGROUND/AIMS: Real-life anti-vascular endothelial growth factor (VEGF) therapy use in patients with wet age-related macular degeneration (wAMD) was assessed in a retrospective, observational study in Canada, France, Germany, Ireland, Italy, the Netherlands, UK and Venezuela.

METHODS: Medical records of patients with wAMD, who started ranibizumab treatment between 1 January 2009 and 31 August 2009, were evaluated. Data were collected until the end of treatment and/or monitoring or until 31 August 2011.

RESULTS: 2227 patients who received ≥ 1 anti-VEGF injection with a baseline visual acuity assessment and ≥ 1 postbaseline visual acuity assessment for the treated eye were evaluated. Visual acuity improved until about day 120; thereafter, visual acuity gains were not maintained. Mean change in visual acuity score from baseline to years 1 and 2 was +2.4 and +0.6 letters, respectively. Patients received a mean of 5.0 and 2.2 injections in the first and second year, respectively. There were substantial differences in visual outcomes and injection frequency between countries. More frequent visits and injections were associated with greater improvements in visual acuity.

CONCLUSIONS: In clinical practice, fewer injections are administered than in clinical trials. Anti-VEGF treatment resulted in an initial improvement in visual acuity; however, this was not maintained over time.

PMID: 25193672 [PubMed - as supplied by publisher]

Int Ophthalmol. 2014 Sep 6. [Epub ahead of print]

Significant reduction of diabetic macular edema following intravitreal ranibizumab injection in the fellow eye.

Rotsos T, Symeonidis C, Triantafillopoulou I, Kanellopoulos S, Kouris A.

Abstract: A significant therapeutic effect in the fellow eye after intravitreal ranibizumab injections was observed in a 39-year-old diabetic male. The patient was followed-up with fluorescein angiography (FA)

and Optical Coherence Tomography (OCT). On referral, best-corrected visual acuity (BCVA) was 6/60 in the right eye and Counting Fingers in the left eye. FA revealed foveal leakage in both eyes. OCT revealed diabetic and cystoid macular edema (DME-CME) in both eyes. The patient was treated with two intravitreal ranibizumab injections in the left eye. BCVA was 6/15 and 6/30 one month after the last injection. OCT revealed significant improvement (DME elimination and significant CME improvement) in both eyes, despite the fact that only the left eye was treated. It is conceivable that, in this eye, chronic vascular damage was limited and a minimal quantity of ranibizumab had a positive effect on vascular permeability, resulting in DME resolution.

PMID: 25192913 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2014 Sep 4. pii: IOVS-14-14293. doi: 10.1167/iov.14-14293. [Epub ahead of print]

A quantitative approach to identify morphological features relevant for visual function in ranibizumab therapy of neovascular AMD.

Roberts P, Mittermueller TJ, Montuoro A, Sulzbacher F, Munk MR, Sacu S, Schmidt-Erfurth U.

Purpose: To quantitatively analyze morphological features in eyes with neovascular age-related macular degeneration (nAMD) at baseline, after 12 months and after 24 months of intravitreal ranibizumab treatment and to perform a structure/function correlation.

Design: Observational case series **Methods:** Eyes with treatment-naïve nAMD were treated with intravitreal ranibizumab according to a standardized dosing regimen over two years and followed continuously in a prospective study design. The central foveal area of 1000µm (horizontal) x 960µm (vertical) of SD-OCT volume scans was evaluated quantitatively (using proprietary software) for the following pathologies: Alteration of the external limiting membrane (ELM), alteration of the ellipsoid zone, subretinal fluid, pigment epithelium detachment, drusen, intraretinal cysts, subretinal mass and sub-retinal pigment epithelium mass. The total area of each pathology was calculated in mm² at baseline and after one and two years of ranibizumab-therapy and correlated with BCVA results.

Results: In total, 480 central SD-OCT scans of 20 consecutive patients were evaluated. In the multivariate regression analysis the area of ELM alteration, the area of intraretinal cysts and foveal retinal thickness were significant variables influencing visual acuity at baseline ($R = -0.827$; $R^2 = 0.684$; $p < 0.001$). The area of ELM alteration was the only significant factor to be directly associated with visual acuity at 12 months ($R = -0.846$; $R^2 = 0.716$; $p < 0.001$) and 24 months ($R = -0.778$; $R^2 = 0.606$; $p < 0.001$).

Conclusions: The integrity of the ELM appears to be the most important feature correlating with visual acuity in native nAMD as well as nAMD treated with intravitreal ranibizumab at each time interval, but not prospectively. In general, no significant predictors for an individual gain or loss in mid- (12 months) or long-term BCVA-results (24 months) were found by OCT.

PMID: 25190663 [PubMed - as supplied by publisher]

J Ocul Pharmacol Ther. 2014 Sep 4. [Epub ahead of print]

Intravitreal Tanibirumab, a Fully Human Monoclonal Antibody Against Vascular Endothelial Growth Factor Receptor 2, Partially Suppresses and Regresses Laser-Induced Choroidal Neovascularization in a Rat Model.

Kim J, Kim TE, Kim JA, Yun JH, Sohn S, Shim SR, Lee SH, Kim SJ.

Purpose: The study investigated the effect of intravitreally administered tanibirumab, a fully human monoclonal antibody against vascular endothelial growth factor receptor 2, in a rat model of laser-induced choroidal neovascularization (CNV).

Methods: CNV was induced by laser photocoagulation on day 0 in the eyes of Brown Norway rats. Intravitreal injection of tanibirumab or phosphate-buffered saline (PBS) was done on day 0 (prevention arm) or day 7 (treatment arm). Seven days after injection, the eyes were enucleated and retinal pigment epithelium-choroid-sclera flat mounts were prepared. Areas of CNV were determined in the flat mounts using tetramethylrhodamine isothiocyanate Bandeiraea simplicifolia (BS) isolectin labeling and intravenously administered fluorescein isothiocyanate-dextran and quantified using an image analysis program.

Results: In the prevention arm, the mean area of CNV measured by BS isolectin labeling was reduced by 28.2% and 53.9% in tanibirumab-treated eyes (20 and 60 µg, respectively) compared with PBS-treated control eyes on day 7 ($P=0.038$ and $P<0.001$, respectively). In the treatment arm, the mean area of CNV measured by BS isolectin labeling was reduced by 28.7% and 46.0% in tanibirumab-treated eyes (20 and 60 µg, respectively) compared with PBS-treated control eyes on day 14 ($P=0.048$ and $P<0.001$,

Conclusions: Intravitreally administered tanibirumab partially suppressed the formation of new CNV and partially regressed preformed laser-induced CNV in the rat model. Tanibirumab may be a feasible treatment for CNV associated with age-related macular degeneration or other causes.

PMID: 25188901 [PubMed - as supplied by publisher]

Arch Soc Esp Oftalmol. 2014 Aug 27. pii: S0365-6691(14)00210-X. doi: 10.1016/j.oftal.2014.05.010. [Epub ahead of print]

Intravitreal injections: What do patients prefer? Analysis of patient's satisfaction and preferences about where to perform intravitreal injections. [Article in English, Spanish]

Rodríguez Ramírez M, Del Barrio Manso MI, Martín Sánchez MD.

OBJECTIVE: To analyse satisfaction and patient preferences on the location where they receive an intravitreal injection.

METHOD: A survey was conducted with the intention of analysing these patients who attended the macula clinic and have been intervened using an intravitreal injection at least once in the day hospital or in the theatre setting, comparing both locations.

RESULTS: The majority of the interviewed patients preferred the day hospital (50.0 versus 37.5%), mostly because of the comfort and the quick service. In patients with severe age-related macular degeneration (AMD) the option is reversed. The overall satisfaction level was positive in both cases (with 87.5% of patients satisfied or very satisfied in the day hospital and 91.1% in the theatre setting). Through the analysis of different aspects of clinical care the assessment was the same or superior for 75.0% of these patients, except in the waiting time. There were no cases of endophthalmitis.

CONCLUSION: In general, patients prefer the clinical intervention in the consulting room than in the theatre setting because of the quicker service. There are several characteristics that can influence this choice and should be taken into account.

PMID: 25176313 [PubMed - as supplied by publisher]

Int Ophthalmol. 2014 Sep 4. [Epub ahead of print]

Ocular pulse amplitude and retinal vessel caliber changes after intravitreal ranibizumab.

Pekel G, Acer S, Cetin EN, Yağcı R, Kaşıkçı A, Cevik A.

Abstract: The purpose of the present study was to examine the effects of intravitreal ranibizumab on ocular pulse amplitude (OPA) and retinal vessel caliber (RVC) in wet age-related macular degeneration (AMD). Thirty-two eyes of 32 wet AMD patients were included in this case series. Three consecutive monthly

injections of ranibizumab were performed. The OPA was measured with the Pascal dynamic contour tonometer. RVC measurements were taken with spectral-domain optical coherence tomography. Pre-injection mean OPA value was 2.55 ± 0.76 mmHg and post-injections mean OPA value was 2.79 ± 0.88 mmHg at the last visit ($p = 0.10$). Pre-injection mean arteriole and venule RVC were 96.7 ± 9.4 and 125.9 ± 8.4 μm ; while post-injections arteriole and venule RVC were 96.0 ± 8.7 and 125.6 ± 8.9 μm , respectively ($p > 0.05$). OPA and RVC are unchanged after triple intravitreal ranibizumab injections, indicating that this treatment does not significantly alter gross retina-choroidal vasculature and hemodynamics.

PMID: 25186317 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Invest Ophthalmol Vis Sci. 2014 Sep 4. pii: IOVS-14-14723. doi: 10.1167/iovs.14-14723. [Epub ahead of print]

Association of Focal Choroidal Excavation with Age-related Macular Degeneration.

Kuroda Y, Tsujikawa A, Ooto S, Yamashiro K, Oishi A, Nakanishi H, Kumagai K, Hata M, Arichika S, Ellabban AA, Yoshimura N.

Purpose: To study the prevalence, tomographic features, and clinical characteristics of focal choroidal excavation (FCE) in eyes with exudative age-related macular degeneration (AMD).

Methods: We examined 243 consecutive eyes with exudative AMD with a prototype swept-source optical coherence tomography (OCT) system. Three-dimensional images of the macular area, covering 6×6 mm², were reconstructed by segmentation of the outer surface of the retinal pigment epithelium.

Results: Three-dimensional swept-source OCT revealed 15 excavations in 12 eyes (4.9%)-10 had a single excavation and two had multiple excavations (2 and 3 excavations). In multi-averaged scans, unusual choroidal tissue was found beneath 5 excavations, bridging the excavation with the outer choroidal boundary. Additionally, the suprachoroidal space was observed beneath 7 excavations-the outer choroidal boundary appeared to be pulled inward by this bridging tissue. In 9 excavations, color fundus photographs showed pigmentary disturbance. Fourteen excavations (93.3%) were located within or adjacent to the choroidal neovascularization area. Compared with eyes without FCE, in eyes with FCE, the mean age was significantly higher ($P = 0.040$) and mean visual acuity was significantly better ($P = 0.014$). In addition, polypoidal lesions were observed in 8 of 12 eyes with FCE, but they appeared to have a limited effect on either the rate of FCE ($P = 0.44$) or the clinical characteristics of the eyes.

Conclusions: Although FCE might be partly related to the development of choroidal neovascularization associated with exudative AMD, its role appears limited to some eyes.

PMID: 25190653 [PubMed - as supplied by publisher]

Stem Cells. 2014 Sep 2. doi: 10.1002/stem.1824. [Epub ahead of print]

Daylight vision repair by cell transplantation.

Santos-Ferreira T, Postel K, Stutzki H, Kurth T, Zeck G, Ader M.

Abstract: Human daylight vision depends on cone photoreceptors and their degeneration results in visual impairment and blindness as observed in several eye diseases including age-related macular degeneration, cone-rod dystrophies, or late stage retinitis pigmentosa, with no cure available. Pre-clinical cell replacement approaches in mouse retina have been focusing on rod dystrophies, due to the availability of sufficient donor material from the rod-dominated mouse retina, leaving the development of treatment options for cone degenerations not well studied. Thus, an abundant and traceable source for donor cone-like photoreceptors was generated by crossing neural retina leucine zipper-deficient (Nrl^{-/-}) mice with an ubiquitous GFP

reporter line resulting in double transgenic tg(Nrl^{-/-}; aGFP) mice. In Nrl^{-/-} retinas all rods are converted into cone-like photoreceptors that express CD73 allowing their enrichment by CD73-based magnetic activated cell sorting prior transplantation into the subretinal space of adult wild-type, cone-only (Nrl^{-/-}) or cone photoreceptor function loss 1 (Cpfl1) mice. Donor cells correctly integrated into host retinas, acquired mature photoreceptor morphology, expressed cone-specific markers and survived for up to six months, with significantly increased integration rates in the cone-only Nrl^{-/-} retina. Individual retinal ganglion cell recordings demonstrated the restoration of photopic responses in cone degeneration mice following transplantation suggesting, for the first time, the feasibility of daylight vision repair by cell replacement in the adult mammalian retina. Stem Cells 2014.

PMID: 25183393 [PubMed - as supplied by publisher]

BMC Med Inform Decis Mak. 2014 Aug 31;14(1):80. [Epub ahead of print]

A survey on computer aided diagnosis for ocular diseases.

Zhang Z, Srivastava R, Liu H, Chen X, Duan L, Wong DW, Kwok CK, Wong TY, Liu J.

BACKGROUND: Computer Aided Diagnosis (CAD), which can automate the detection process for ocular diseases, has attracted extensive attention from clinicians and researchers alike. It not only alleviates the burden on the clinicians by providing objective opinion with valuable insights, but also offers early detection and easy access for patients.

METHOD: We review ocular CAD methodologies for various data types. For each data type, we investigate the databases and the algorithms to detect different ocular diseases. Their advantages and shortcomings are analyzed and discussed.

RESULT: We have studied three types of data (i.e., clinical, genetic and imaging) that have been commonly used in existing methods for CAD. The recent developments in methods used in CAD of ocular diseases (such as Diabetic Retinopathy, Glaucoma, Age-related Macular Degeneration and Pathological Myopia) are investigated and summarized comprehensively.

CONCLUSION: While CAD for ocular diseases has shown considerable progress over the past years, the clinical importance of fully automatic CAD systems which are able to embed clinical knowledge and integrate heterogeneous data sources still show great potential for future breakthrough.

PMID: 25175552 [PubMed - as supplied by publisher]

Klin Monbl Augenheilkd. 2014 Sep;231(9):874-82. doi: 10.1055/s-0034-1382853. Epub 2014 Sep 2.

**[Surgery for age-related macular degeneration. Still an option in the age of pharmacotherapy?].
[Article in German]**

Joussen AM, Kirchhof B.

Abstract: This review assesses the relevance of surgical approaches for age-related macular degeneration (AMD) with respect to the pathophysiology of AMD and the current pharmacological possibilities. We discuss the different surgical approaches such as subretinal membrane excision, cell transplantation (IPE and RPE) and transplantation of retina and choroid (PATCH), as well as translocation surgery. Peeling of epiretinal membranes in patients with drusen as well as vitrectomy before epiretinal brachytherapy (VIDEON system) are the final topics. While overall pharmacotherapy has displaced surgical approaches, surgery is worthy of consideration in selected cases. For these patients surgical options need to be maintained in the armamentarium of retinal surgeons.

PMID: 25181504 [PubMed - in process]

Pathogenesis

Exp Brain Res. 2014 Sep 3. [Epub ahead of print]

The role of glial cells and the complement system in retinal diseases and Alzheimer's disease: common neural degeneration mechanisms.

Harvey H, Durant S.

Abstract: Many age-related degenerative diseases of the central nervous system (CNS) increasingly appear to have similarities in their underlying causes. By applying knowledge between disorders, and in particular between degenerative diseases of different components of the CNS (e.g. the eye and the brain), we can begin to elucidate general mechanisms of neural degeneration. Age-related macular degeneration and glaucoma, two diseases of retinal neurons, which have recently been discussed in view of their common mechanisms with Alzheimer's disease, highlight this perspective. This review discusses the common roles of the complement system (an immunological system) and glial cells (providing, amongst other functions, trophic support to neurons) in these three disorders. A number of facets of these systems would seem to be involved in the mechanisms of degeneration in at least two of the three diseases considered here. Regulatory proteins of the complement system (such as factor H), neurotrophin levels, and the interaction of microglia with the complement system in particular may be general to all three presentations of neural degeneration. Investigating the functioning of these fundamental systems across different diseases exemplifies the importance of considering advances in knowledge across a wider base than specific disease pathology. This may give insights both for understanding the function of these supporting systems and providing an avenue for developing future therapeutic targets general to neural degenerative diseases.

PMID: 25183160 [PubMed - as supplied by publisher]

J Fr Ophtalmol. 2014 Sep 1. pii: S0181-5512(14)00210-1. doi: 10.1016/j.jfo.2014.06.001. [Epub ahead of print]

[Review and expert opinion in age related macular degeneration. Focus on the pathophysiology, angiogenesis and pharmacological and clinical data.] [Article in French]

Weber M, Sennlaub F, Souied E, Cohen SY, Béhar-Cohen F, Milano G, Tadayoni R.

Abstract: Age related macular degeneration (AMD) is a pathological aging of the macula, brought about by the interaction of genetic and environmental factors. It induces geographic atrophy of the retina and/or choroidal neovascularization. In the latter, abnormal vessels develop from the choriocapillaris, with the involvement of VEGF (vascular endothelial growth factor). The VEGF family includes several factors, including VEGF-A, B, C, D, F and PlGF (placental growth factor). Their biological properties and their affinities to the VEGFR1, VEGFR2 and VEGFR3 receptors found on endothelial cells differ. Exudative AMD involves mainly VEGF-A and VEGF-R2. Anti-VEGF agents used in ophthalmology (ranibizumab, bevacizumab and aflibercept) are designed to primarily target this pathway. In vitro, all have sufficient affinity to their ligands. Their therapeutic efficacy must therefore be judged based on clinical criteria. In clinical practice, the minimum number of injections required for a satisfactory result appears to be comparable with all the three. The few available studies on therapeutic substitutions of anti-VEGF compounds suggest that some patients may benefit from substituting the anti-VEGF in cases of an unsatisfactory response to an initial molecule. Although local side effects, including increased risk of geographic atrophy, and systemic effects, including vascular accidents, have been suggested, these risks remain low, specially compared to the benefits of the treatment. Differences in safety between anti-VEGF are theoretically possible but unproven.

PMID: 25190312 [PubMed - as supplied by publisher]

Open Ophthalmol J. 2014 Jul 23;8:39-47. doi: 10.2174/1874364101408010039. eCollection 2014.

Glycolysis in patients with age-related macular degeneration.

Yokosako K, Mimura T, Funatsu H, Noma H, Goto M, Kamei Y, Kondo A, Matsubara M.

PURPOSE: Retinal adenosine triphosphate is mainly produced via glycolysis, so inhibition of glycolysis may promote the onset and progression of age-related macular degeneration (AMD). When glycolysis is inhibited, pyruvate is metabolized by lactic acid fermentation instead of entering the mitochondrial tricarboxylic acid (TCA) cycle. We measured urinary pyruvate and lactate levels in patients with AMD.

METHODS: Eight patients with typical AMD (tAMD group) and 9 patients with polypoidal choroidal vasculopathy (PCV group) were enrolled. Urinary levels of pyruvate, lactate, α -hydroxybutyrate, and β -hydroxybutyrate were measured in all patients.

RESULTS: The mean urinary levels of pyruvate and lactate were 8.0 ± 2.8 and 7.5 ± 8.3 $\mu\text{g}/\text{mg}$ creatinine (reference values: 0.5-6.6 and 0.0-1.6), respectively, with the mean increase over the reference value being $83.6 \pm 51.1\%$ and $426.5 \pm 527.8\%$, respectively. In 12 patients (70.6%), the lactate/pyruvate ratio was above the reference range. Urinary levels of α -hydroxybutyrate and β -hydroxybutyrate were decreased by $-31.9 \pm 15.2\%$ and $-33.1 \pm 17.5\%$ compared with the mean reference values. There were no significant differences of any of these glycolysis metabolites between the tAMD and PCV groups. Multivariate analysis revealed that none of the variables tested, including patient background factors (age, hypertension, diabetes, hyperlipidemia, cerebrovascular disease, alcohol, smoking, visual acuity, and AMD phenotype), were significantly associated with the lactate/pyruvate ratio.

CONCLUSION: A high lactate/pyruvate ratio is a well-known marker of mitochondrial impairment, and it indicates poor oxidative function in AMD. Our results suggest that increased lactate levels may be implicated in the pathogenesis of AMD.

PMID: 25191529 [PubMed] PMCID: PMC4150380

Biosci Rep. 2014 Sep 4. [Epub ahead of print]

New functional and structural insights from updated mutational databases for complement factor H, factor I, membrane cofactor protein and C3.

Rodriguez E, Rallapalli PM, Osborne A, Perkins SJ.

Abstract: Atypical haemolytic uraemic syndrome, age-related macular degeneration and other diseases are associated with defective alternative pathway (AP) regulation. Factor H (CFH), Factor I (CFI), membrane cofactor protein (MCP) and C3 exhibited the most disease-associated genetic alterations in the AP. Our interactive structural database for these was updated with a total of 317 genetic alterations. A consensus structure for the short complement regulator (SCR) domain showed that the majority (37%) of SCR mutations occurred at its hypervariable loop and its four conserved Cys residues. Mapping 111 missense mutations onto the CFH structure showed that over half occurred in the C-terminal domains SCR-15 to SCR-20. In particular, SCR-20 with the highest total of affected residues is associated with binding to C3d and heparin-like oligosaccharides. No clustering of 48 missense mutations in CFI was seen. In MCP, SCR-3 was the most affected by 23 missense mutations. In C3, the neighbouring thioester and macroglobulin domains exhibited most of 46 missense mutations. The mutations in the regulators CFH, CFI and MCP involve loss-of-function while those for C3 involve gain-of-function. This combined update emphasizes the importance of the complement AP in inflammatory disease, clarifies the functionally-important regions in these proteins, and will facilitate diagnosis and therapy.

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PLoS One. 2014 Sep 4;9(9):e106507. doi: 10.1371/journal.pone.0106507. eCollection 2014.

Characterization of a spontaneous retinal neovascular mouse model.

Hasegawa E, Sweigard H, Husain D, Olivares AM, Chang B, Smith KE, Birsner AE, D'Amato RJ, Michaud NA, Han Y, Vavvas DG, Miller JW, Haider NB, Connor KM.

BACKGROUND: neovascular age-related macular degeneration (AMD), whereby abnormal blood vessels develop in the retina leading to debilitating vision loss and eventual blindness. The novel mouse strain, neoretinal vascularization 2 (NRV2), shows spontaneous fundus changes associated with abnormal neovascularization. The purpose of this study is to characterize the induction of pathologic angiogenesis in this mouse model.

METHODS: The NRV2 mice were examined from postnatal day 12 (p12) to 3 months. The phenotypic changes within the retina were evaluated by fundus photography, fluorescein angiography, optical coherence tomography, and immunohistochemical and electron microscopic analysis. The pathological neovascularization was imaged by confocal microscopy and reconstructed using three-dimensional image analysis software.

RESULTS: We found that NRV2 mice develop multifocal retinal depigmentation in the posterior fundus. Depigmented lesions developed vascular leakage observed by fluorescein angiography. The spontaneous angiogenesis arose from the retinal vascular plexus at postnatal day (p)15 and extended toward retinal pigment epithelium (RPE). By three months of age, histological analysis revealed encapsulation of the neovascular lesion by the RPE in the photoreceptor cell layer and subretinal space.

CONCLUSIONS: The NRV2 mouse strain develops early neovascular lesions within the retina, which grow downward towards the RPE beginning at p15. This retinal neovascularization model mimics early stages of human retinal angiomatous proliferation (RAP) and will likely be a useful in elucidating targeted therapeutics for patients with ocular neovascular disease.

PMID: 25188381 [PubMed - in process]

Pathology. 2014 Oct;46 Suppl 2:S30. doi: 10.1097/01.PAT.0000454185.97418.8c.

Ophthalmologic Pathology: SY20-1 OCULAR PATHOLOGY, AN OVERVIEW: RETINA AND OPTIC NERVE.

Cummings TJ.

Abstract: The goal of this symposium is to present an overview of ocular pathology, and this lecture is dedicated to an overview of the pathology of the retina and optic nerve. The retina is a complex tissue lining the inner surface of the eye. It receives images from the outside world and transmits signals to the visual cortex in the occipital pole of the brain. The retina is basically neuroglial tissue, composed of ganglion cells (neurons) and glia (astrocytes within the nerve fiber layer and ganglion cell layer, and, Müller radial glia which extend from the inner limiting membrane to the outer limiting membrane). The pathology of some retinal disorders, including retinoblastoma, hemangioblastoma, and age-related macular degeneration, will be presented. The optic nerve is a white matter tract containing glia and axons, but not ganglion cells or Schwann cells. The axons originate from the retinal ganglion cells and course posteriorly within the retinal nerve fiber layer. Optic nerve pathology including optic nerve gliomas, optic nerve meningiomas, optic nerve choristoma, demyelinating disease, granulomatous inflammation, and ischemia, will be presented.

PMID: 25188127 [PubMed - in process]

J Pathol. 2014 Sep 4. doi: 10.1002/path.4433. [Epub ahead of print]

Aryl hydrocarbon receptor knockout exacerbates choroidal neovascularization via multiple pathogenic pathways.

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Choudhary M, Kazmin D, Hu P, Thomas RS, McDonnell DP, Malek G.

Abstract: The aryl hydrocarbon receptor (AhR) is a heterodimeric transcriptional regulator with pleiotropic functions in xenobiotic metabolism and detoxification, vascular development and cancer. Herein, we report a previously undescribed role for the AhR signaling pathway in the pathogenesis of the wet, neovascular, sub-type of age-related macular degeneration (AMD), the leading cause of vision loss in the elderly in the Western World. Comparative analysis of gene expression profiles of aged AhR^{-/-} and wild-type (wt) mice using high-throughput RNA sequencing revealed differential modulation of genes belonging to several AMD-related pathogenic pathways including inflammation, angiogenesis and extracellular matrix regulation. To investigate AhR regulation of these pathways in wet AMD, we experimentally-induced choroidal neovascular lesions in AhR^{-/-} mice and found they measured significantly larger in area and volume compared to age-matched wt mice. Furthermore, these lesions displayed a higher number of ionized calcium-binding adaptor molecule 1 positive (Iba1+) microglial cells and a greater amount of collagen type IV deposition, events also seen in human wet AMD pathology specimens. Consistent with our in vivo observations, AhR knockdown was sufficient to increase choroidal endothelial cell migration and tube formation in vitro. Moreover, AhR knockdown caused an increase in collagen type IV production and secretion in both retinal pigment epithelial (RPE) and choroidal endothelial cell cultures, increased expression of angiogenic and inflammatory molecules including vascular endothelial growth factor A (VEGFA) and chemokine (C-C motif) ligand 2 (CCL2) in RPE cells, and increased expression of secreted phosphoprotein 1 (SPP1) and transforming growth factor, beta 1 (TGFB1) in choroidal endothelial cells. Collectively, our findings identify AhR as a regulator of multiple pathogenic pathways in experimentally-induced choroidal neovascularization, findings that are consistent with a possible role of AhR in wet AMD.

PMID: 25186463 [PubMed - as supplied by publisher]

J Clin Invest. 2014 Sep 2. pii: 74527. doi: 10.1172/JCI74527. [Epub ahead of print]

Targeting VE-PTP activates TIE2 and stabilizes the ocular vasculature.

Shen J, Frye M, Lee BL, Reinardy JL, McClung JM, Ding K, Kojima M, Xia H, Seidel C, Silva RL, Dong A, Hackett SF, Wang J, Howard BW, Vestweber D, Kontos CD, Peters KG, Campochiaro PA.

Abstract: Retinal and choroidal neovascularization (NV) and vascular leakage contribute to visual impairment in several common ocular diseases. The angiopoietin/TIE2 (ANG/TIE2) pathway maintains vascular integrity, and negative regulators of this pathway are potential therapeutic targets for these diseases. Here, we demonstrated that vascular endothelial-protein tyrosine phosphatase (VE-PTP), which negatively regulates TIE2 activation, is upregulated in hypoxic vascular endothelial cells, particularly in retinal NV. Intraocular injection of an anti-VE-PTP antibody previously shown to activate TIE2 suppressed ocular NV. Furthermore, a small-molecule inhibitor of VE-PTP catalytic activity (AKB-9778) activated TIE2, enhanced ANG1-induced TIE2 activation, and stimulated phosphorylation of signaling molecules in the TIE2 pathway, including AKT, eNOS, and ERK. In mouse models of neovascular age-related macular degeneration, AKB-9778 induced phosphorylation of TIE2 and strongly suppressed NV. Ischemia-induced retinal NV, which is relevant to diabetic retinopathy, was accentuated by the induction of ANG2 but inhibited by AKB-9778, even in the presence of high levels of ANG2. AKB-9778 also blocked VEGF-induced leakage from dermal and retinal vessels and prevented exudative retinal detachments in double-transgenic mice with high expression of VEGF in photoreceptors. These data support targeting VE-PTP to stabilize retinal and choroidal blood vessels and suggest that this strategy has potential for patients with a wide variety of retinal and choroidal vascular diseases.

PMID: 25180601 [PubMed - as supplied by publisher]

PLoS One. 2014 Sep 3;9(9):e106421. doi: 10.1371/journal.pone.0106421. eCollection 2014.

The Oxidative Stress Product Carboxyethylpyrrole Potentiates TLR2/TLR1 Inflammatory Signaling in Macrophages.

Saeed AM, Duffort S, Ivanov D, Wang H, Laird JM, Salomon RG, Cruz-Guilloty F, Perez VL.

Abstract: Oxidative stress is key in the pathogenesis of several diseases including age-related macular degeneration (AMD), atherosclerosis, diabetes, and Alzheimer's disease. It has previously been established that a lipid peroxidation product, carboxyethylpyrrole (CEP), accumulates in the retinas of AMD patients. Retinal infiltrating macrophages also accumulate in the retinas of both AMD patients and in a murine model of AMD. We therefore investigated the ability of CEP-adducts to activate innate immune signaling in murine bone-marrow derived macrophages (BMDMs). We found that CEP specifically synergizes with low-dose TLR2-agonists (but not agonists for other TLRs) to induce production of inflammatory cytokines. Moreover, CEP selectively augments TLR2/TLR1-signaling instead of TLR2/TLR6-signaling. These studies uncover a novel synergistic inflammatory relationship between an endogenously produced oxidation molecule and a pathogen-derived product, which may have implications in the AMD disease process and other oxidative stress-driven pathologies.

PMID: 25184331 [PubMed - in process] PMCID: PMC4153630

Epidemiology

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Prevalence of Age-related Macular Degeneration in an Elderly Urban Chinese Population in China: The Jiangning Eye Study.

Ye H, Zhang Q, Liu X, Cai X, Yu W, Yu S, Wang T, Lu W, Li X, Jin H, Hu Y, Kang X, Zhao P.

PURPOSE: To describe the prevalence of age-related macular degeneration (AMD) in an elderly urban Chinese population in China.

METHODS: A population-based cross-sectional study was conducted using a cluster random sample of residents aged 50 years or older living in the Jiangning Road Sub-district, Jing'an District, Shanghai, China. All participants underwent a standardized interview and comprehensive eye examinations, including digital retinal photography and spectral domain optical coherence tomography (OCT) examinations of both eyes between November 2012 and February 2013. Trained graders assessed the presence and severity of AMD lesions based on a modified version of the Wisconsin Age-Related Maculopathy Grading System.

RESULTS: Of the 2044 subjects who participated (82.5% response rate), 2005 had fundus photographs and OCT results of sufficient quality for grading of AMD signs. Early and late AMD were present in 206 (10.3%) and 23 (1.1%) participants, respectively. After age standardization, the prevalence of early AMD in Chinese persons aged 50 years or older was 9.5% (95% confidence interval [CI], 8.2-10.8) and that of late AMD was 1.0% (95% CI, 0.5-1.5).

CONCLUSIONS: The prevalence of early and late AMD in this urban Chinese sample was higher than that reported in the Beijing and Handan studies. AMD is highly prevalent among the elderly urban Chinese population in mainland China.

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Genetics

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Association between variants A69S in ARMS2 gene and response to treatment of exudative AMD: a meta-analysis.

Hu Z, Xie P, Ding Y, Yuan D, Liu Q.

Abstract: A study was undertaken to investigate the association between A69S in age-related maculopathy susceptibility 2 (ARMS2) and the response to anti-angiogenesis treatment in exudative age-related macular degeneration (AMD). A literature-based meta-analysis was performed of studies relevant to A69S and the response to anti-angiogenesis treatment. PubMed, Web of Science, China National Knowledge Infrastructure (CNKI) and Sinomed databases were used to retrieve articles up to July 2014. Pooled ORs and 95% CIs were estimated using fixed and random effects models in Stata V.9.0. Q-statistic testing was used to assess heterogeneity. Twelve articles comprising 2389 cases were included in the final meta-analysis. The analysis of the overall population indicated a statistically significant association between A69S and the response to anti-angiogenesis treatment in exudative AMD (GG vs TT: OR 1.34 (95% CI 1.01 to 1.77), $p=0.039$; GT vs TT: OR 1.58 (95% CI 1.08 to 2.31), $p=0.018$; GG+GT vs TT: OR 1.74 (95% CI 1.19 to 2.52), $p=0.004$). In subgroup analysis, A69S appeared more likely to be a predictor for anti-angiogenic response in the East Asian population (GG vs TT: OR 1.65 (95% CI 1.02 to 2.68), $p=0.042$; GT vs TT: OR 1.66 (95% CI 1.17 to 2.37), $p=0.005$; GG+GT vs TT: OR 1.82 (95% CI 1.07 to 3.10), $p=0.027$; G vs T: OR 1.56 (95% CI 1.01 to 2.41)). However, no statistical significance was found in the Caucasian subgroup analysis. This study shows an association between A69S polymorphism in the ARMS2 gene and the anti-angiogenesis treatment response. A69S could be considered predictive of the anti-angiogenic effects, especially in Asian populations.

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