Drug treatment


Nikkhah H, Karimi S, Ahmadieh H, et al

Purpose: To provide the clinical recommendations for the administration of intravitreal anti-vascular endothelial growth factor (VEGF) drugs especially bavacizumab for ocular vascular diseases including diabetic macular edema, neovascular age-related macular degeneration, myopic choroidal neovascularization, retinal vein occlusion and central serous chorioretinopathy.

Methods: Twenty clinical questions were developed by the guideline technical committee. Relevant websites and databases were searched to find out the pertinent clinical practice guidelines to answer the questions. The technical committee provided possible answers (scenarios) according to the available evidences for each question. All scenarios along with their levels of evidence and the supported articles were sent to the experts for external review. If the experts did not agree on any of the scenarios for one particular clinical question, the technical committee reviewed all scenarios and their pertinent evidences and made the necessary decision. After that, the experts were asked to score them again. All confirmed scenarios were gathered as the final recommendations.

Results: All the experts agreed on at least one of the scenarios. The technical committee extracted the agreed scenario for each clinical question as the final recommendation. Finally, 56 recommendations were developed for the procedure of intravitreal anti-VEGF injection and their applications in the management of ocular vascular diseases.

Conclusion: The implementation of this guideline can standardize the management of the common ocular vascular diseases by intravitreal injection of anti-VEGF agents. It can lead to better policy-making and evidence-based clinical decision by ophthalmologists and optimal evidence based eye care for patients.

PMID: 29719645 PMCID: PMC5905310 DOI: 10.4103/jovr.jovr_50_18


Central corneal thickness and intraocular pressure before the intravitreal administration of ranibizumab and in the early period following the injection.
Biatas-Niedziela D, Olechowski A, Ciszewska J, Switka-Wiectawska I, Kecik D.

Abstract: The aim of the study was to determine the differences in the central corneal thickness and intraocular pressure measured before intravitreal administration of ranibizumab and at 30 to 60 minutes after the injection. The intraocular pressure was analysed as a stand-alone parameter and in correlation with the central corneal thickness. 72 patients (144 eyes) were enrolled. The treated eyes were compared to the fellow, non-treated eyes. The mean central corneal thickness in a treated eye was 558 μm and 596 μm at baseline (before the injection) and after the injection, respectively (p<0.05). The mean intraocular pressure not correlated to the central corneal thickness in a treated eye 15.29 mmHg and 16.83 mmHg at baseline and post-injection, respectively (p<0.05). When assessed in correlation with the central corneal thickness, the intraocular pressure did not increase post-injection in the treated eyes.

PMID: 29715401


Foveal threshold and photoreceptor integrity for prediction of visual acuity after intravitreal aflibercept on age-related macular degeneration.

Sakai T, Okude S, Tsuneoka H.

Purpose: To determine whether baseline foveal threshold and photoreceptor integrity can predict best-corrected visual acuity (BCVA) at 12 months after intravitreal aflibercept (IVA) therapy in eyes with neovascular age-related macular degeneration (AMD).

Patients and methods: We evaluated 25 eyes of 25 patients with treatment-naïve neovascular AMD who received IVA once a month for 3 months, followed by once every 2 months for 8 months. BCVA, integrity of the external limiting membrane (ELM) or the ellipsoid zone (EZ) of the photoreceptors, and retinal sensitivity were determined before (baseline) and at 6 and 12 months after initial IVA. The average threshold foveal sensitivity and mean deviation within the central 10° were determined by Humphrey central 10-2 perimetry. Correlations between BCVA at 12 months and integrity of the ELM or EZ, foveal threshold, and mean deviation at each visit were determined.

Results: At 12 months, BCVA improved significantly from 0.20±0.23 to 0.10±0.22 logMAR (logarithm of the minimum angle of resolution) units, and foveal threshold and mean deviation improved significantly from 29.0±5.1 and -3.38±3.10 dB to 32.6±3.2 and -1.64±2.10 dB, respectively (P=0.0009 and P=0.0021). At baseline, both foveal threshold and integrity of the ELM were significantly correlated with BCVA at 12 months (P=0.0428 and P=0.0275).

Conclusion: These results indicate that both integrity of the ELM and foveal threshold at baseline can predict BCVA after treatment for neovascular AMD. There is a possibility that these parameters can predict the efficacy of IVA in each case.

PMID: 29713139 PMCID: PMC5907895 DOI: 10.2147/OPTH.S156162


Development of facile drug delivery platform of ranibizumab fabricated PLGA-PEGylated magnetic nanoparticles for age-related macular degeneration therapy.

Yan J, Peng X, Cai Y, Cong W.

Abstract: The present anti-angiogenic therapies for neovascular age-related macular degeneration require effective drug delivery systems for transfer drug molecules. Ranibizumab is an active humanized monoclonal antibody that counteracts active forms of vascular endothelial growth factor A in the
neovascular age-related macular degeneration therapy. The development of ranibizumab-related therapies, we have designed the effective drug career with engineered magnetic nanoparticles (Fe3O4) as a facile platform of ranibizumab delivery for the treatment of neovascular age-related macular degeneration. Ranibizumab conjugated iron oxide (Fe3O4)/PEGylated poly lactide-co-glycolide (PEG-PLGA) was successfully designed and the synthesized materials are analyzed different analytical techniques. The microscopic techniques (Scanning Electron Microscopy (SEM) & Transmission Electron Microscopy (TEM)) are clearly displayed that spherical nanoparticles into the PEG-PLGA matrix and presence of elements and chemical interactions confirmed by the results of energy dispersive X-ray analysis (EDX) and Fourier transform infrared (FTIR) spectroscopic methods. The in vitro anti-angiogenic evaluation of Fe3O4/PEG-PLGA polymer nanomaterial efficiently inhibits the tube formation in the Matrigel-based assay method by using human umbilical vein endothelial cells. Ranibizumab treated Fe3O4/PEG-PLGA polymer nanomaterials not disturbed cell proliferation and the results could not display the any significant differences in human endothelial cells. The present investigated results describe that Fe3O4/PEG-PLGA polymer nanomaterials can be highly favorable and novel formulation for the treatment of neovascular age-related macular degeneration.

PMID: 29704861 DOI: 10.1016/j.jphotobiol.2018.04.033

Other treatment and diagnosis


Emixustat Hydrochloride for Geographic Atrophy Secondary to Age-Related Macular Degeneration: A Randomized Clinical Trial.

Rosenfeld PJ, Dugel PU, Holz FG, Heier JS, Pearlman JA, Novack RL, Csaky KG, Koester JM, Gregory JK, Kubota R.

Purpose: To determine whether emixustat hydrochloride (emixustat) reduces the rate of enlargement of geographic atrophy (GA) compared with placebo in subjects with age-related macular degeneration (AMD) and to evaluate the safety and tolerability of emixustat over 24 months of treatment.

Design: Multicenter, randomized, double-masked, placebo-controlled, phase 2b/3 clinical trial.

Participants: Patients with GA secondary to AMD, a visual acuity score of at least 35 letters, and GA with a total area of 1.25 to 18 mm2 were enrolled.

Methods: Subjects were randomized (1:1:1:1) to emixustat 2.5 mg, 5 mg, 10 mg, or placebo, administered orally once daily for 24 months. Visits included screening, baseline, and months 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, and 25.

Main Outcome Measures: The primary efficacy end point was the mean annual growth rate of total GA area in the study eye, as measured by a central reading center using fundus autofluorescence (FAF) images. The change from baseline in normal luminance best-corrected visual acuity (NL-BCVA) was a secondary efficacy end point.

Results: Of 508 randomized subjects, 320 completed the study. Demographics and baseline characteristics were comparable between treatment groups. On average, GA lesions in the study eye grew at a similar rate in each group (emixustat: 1.69 to 1.84 mm2/year; placebo: 1.69 mm2/year; P ≥ 0.81). Changes in NL-BCVA were also comparable between groups. Subjects with a larger low luminance deficit (LLD) at baseline (≥20 letters) demonstrated a more rapid growth of GA over 24 months. No relationship was observed between the risk-allele status of the AMD-associated single-nucleotide polymorphisms tested and the growth rate of GA. The most common adverse events in emixustat-treated subjects were delayed dark adaptation (55%), chromatopsia (18%), visual impairment (15%), and erythropsia (15%).

Conclusions: Emixustat did not reduce the growth rate of GA in AMD. The most common adverse events
were ocular in nature and likely related to the drug's mechanism of action. Data gained from this study over a 2-year period add to the understanding of the natural history of GA and the baseline characteristics affecting the growth rate of GA.

PMID: 29716784 DOI: 10.1016/j.ophtha.2018.03.059


Cell Transplantation for Retinal Degeneration: Transition from Rodent to Nonhuman Primate Models.

McGill TJ, Wilson DJ, Stoddard J, Renner LM, Neuringer M.

Abstract: Transplantation of potentially therapeutic cells into the subretinal space is a promising prospective therapy for the treatment of retinal degenerative diseases including age-related macular degeneration (AMD). In rodent models with photoreceptor degeneration, subretinal transplantation of cell suspensions has repeatedly been demonstrated to rescue behaviorally measured vision, maintain electrophysiological responses from the retina and the brain, and slow the degeneration of rod and cone photoreceptors for extended periods. These studies have led to the initiation of a number of FDA-approved clinical trials for application of cell-based therapy for AMD and other retinal degenerative diseases. However, translation from rodent models directly into human clinical trials skips an important intermediary preclinical step that is needed to address critical issues for intraocular cell transplantation. These include determination of the most appropriate and least problematic surgical approach, the application of treatment in an eye with similar size and structure including the presence of a macula, and a thorough understanding of the immunological considerations regarding graft survival and the consequences of grafted cell rejection. This chapter will review these and related issues and will document current efforts to address these concerns.

PMID: 29721998 DOI: 10.1007/978-3-319-75402-4_78


The iPSc-Derived Retinal Tissue as a Tool to Study Growth Factor Production in the Eye.

Alavi M, Baranov P.

Abstract: Traumatic, inherited, and age-related degenerative diseases of the retina, such as retinal detachment, glaucoma, retinitis pigmentosa, and age-related macular degeneration, are characterized by the irreversible loss of retinal neurons. Several growth factors, including glial cell-derived neurotrophic factor and pigment epithelium-derived factor, have been shown to rescue retinal neurons in animal models of retinal disease. Here we describe a scalable and robust system to study the growth factor induction in the retina: retinal organoids derived from the induced pluripotent stem cells. We have demonstrated that they secrete GDNF and PEDF at the levels tenfold above detection limit for ELISA. We also have shown that growth factor production in this system may be upregulated by specific trigger, demonstrating the feasibility of this approach for drug discovery.

PMID: 29721995 DOI: 10.1007/978-3-319-75402-4_75


Combined VEGF/PDGF inhibition using axitinib induces αSMA expression and a pro-fibrotic phenotype in human pericytes.

Purpose: Large trials on anti-VEGF/PDGF (vascular endothelial/platelet-derived growth factor) combination therapy have been established to improve management of neovascular activity in age-related macular degeneration. Targeting pericytes, PDGF is thought to induce vessel regression and reduce fibrovascular scarring. The fate of pericytes exposed to anti-VEGF/PDGF combination therapy is not clear. Therefore, this study was designed to study the influence of anti-VEGF/PDGF on pericyte phenotype and cellular behavior.

Methods: Human pericytes from placenta (hPC-PL) were treated with axitinib, a tyrosine kinase inhibitor targeting VEGFR1-3 and PDGFR. Toxic effects were excluded using live/dead staining. Phenotypic changes were evaluated using phalloidin staining for actin cytoskeleton and the expression of stress fibers. mRNA and protein expression levels of α-smooth muscle actin (αSMA) as a marker of proto-myofibroblastic transition were evaluated with real-time PCR and Western blotting. Influences of fibrotic cellular mechanisms were evaluated with a scratch wound migration and a collagen gel contraction assay.

Results: Treatment with 0.5, 1, and 2.5 μg/ml axitinib strongly induced a proto-myofibroblast-like actin cytoskeleton with a marked increase in stress fibers. Quantitative real-time PCR and Western blotting revealed these changes to be linked to dose-dependent increases in αSMA mRNA and protein expression. However, fibrotic cellular mechanisms were significantly reduced in the presence of axitinib (scratch wound closure: up to -78.4%, collagen gel contraction: up to -37.4%).

Conclusions: Combined anti-VEGF/PDGF inhibition seems to induce a proto-myofibroblast-like phenotype in human pericytes in vitro, but reduce profibrotic cellular mechanisms due to prolonged anti-PDGF inhibition.

PMID: 29721663 DOI: 10.1007/s00417-018-3987-8


Automated Segmentation Methods of Drusen to Diagnose Age-Related Macular Degeneration Screening in Retinal Images.

Kim YJ, Kim KG.

Abstract: Existing drusen measurement is difficult to use in clinic because it requires a lot of time and effort for visual inspection. In order to resolve this problem, we propose an automatic drusen detection method to help clinical diagnosis of age-related macular degeneration. First, we changed the fundus image to a green channel and extracted the ROI of the macular area based on the optic disk. Next, we detected the candidate group using the difference image of the median filter within the ROI. We also segmented vessels and removed them from the image. Finally, we detected the drusen through Renyi’s entropy threshold algorithm. We performed comparisons and statistical analysis between the manual detection results and automatic detection results for 30 cases in order to verify validity. As a result, the average sensitivity was 93.37% (80.95%-100%) and the average DSC was 0.73 (0.3-0.98). In addition, the value of the ICC was 0.984 (CI: 0.967-0.993, p < 0.01), showing the high reliability of the proposed automatic method. We expect that the automatic drusen detection helps clinicians to improve the diagnostic performance in the detection of drusen on fundus image.

PMID: 29721037 PMCID: PMC5867666 DOI: 10.1155/2018/6084798


Direct Photocoagulation Guided by Merged Retinal Images for the Treatment of Focal Diabetic Macular Edema.

Takamura Y, Matsumura T, Arimura S, Gozawa M, Morioka M, YutakaYamada, Inatani M.
Purpose: To introduce a novel laser photocoagulation (PC) protocol named merged image-guided PC (MIG-PC), which included merging the images of the fundus, optical coherence tomography (OCT) map, and fluorescein angiography (FA). We compared the anatomical and functional results between MIG-PC and FA-guided PC (FG-PC) for the treatment of focal diabetic macular edema (DME).

Method: We examined the treatment outcomes in 27 consecutive eyes treated with MIG-PC compared with 28 matched eyes treated with FG-PC. We identified the microaneurysms (MAs) located in the focal edema areas and ablated them using focal PC. Best-corrected visual acuity (BCVA) and retinal thickness (RT) measured using OCT were compared between the groups at baseline and 2, 4, 8, 12, and 24 weeks after treatment.

Results: The foveal and perifoveal RT were reduced after treatment in both the groups, and the perifoveal RT in the MIG-PC group was significantly lower than that in the FG-PC group at 4 weeks and thereafter. BCVA in the MIG-PC group was significantly higher than that in the FG-PC group at 12 and 24 weeks. The numbers of laser spots \( p = 0.0001 \), additional laser treatments \( p = 0.0121 \), and intravitreal injection of ranibizumab \( p = 0.0012 \) in the MIG-PC group were significantly lower than those in the FG-PC group (Mann-Whitney test).

Conclusion: MIG-PC contributed to the improvement in BCVA and reduction in RT, number of laser shots required, and retreatment rates. Based on our data, MIG-PC can be recommended for the treatment of focal DME. This trial is registered with ID UMIN000030390.

PMID: 29721014 PMCID: PMC5867680 DOI: 10.1155/2018/2401094

Ophthalmologe. 2018 Apr 30. [Epub ahead of print]

[Deep learning to support therapy decisions for intravitreal injections]. [Article in German]

Prahs P, Märker D, Mayer C, Helbig H.

Abstract: Significant progress has been made in artificial intelligence and computer vision research in recent years. Machine learning methods excel in a wide variety of tasks where sufficient data are available. We describe the application of a deep convolutional neural network for the prediction of treatment indication with anti-vascular endothelial growth factor (VEGF) medications based on central retinal optical coherence tomography (OCT) scans. The neural network classifier was trained with OCT images acquired during routine treatment at the University of Regensburg over the years 2008-2016. In over 95% of the cases the treatment indication was accurately predicted based on a singular OCT B scan without human intervention. Despite promising classification the results of deep learning techniques, should always be controlled by the treating physician because false classification can never be excluded due to the probabilistic nature of the method.

PMID: 29713804 DOI: 10.1007/s00347-018-0708-y


Optical Coherence Tomography Angiography versus Dye Angiography in Age-Related Macular Degeneration: Sensitivity and Specificity Analysis.

Nikolopoulou E, Lorusso M, Micelli Ferrari L, Cininelli MV, Bandello F, Querques G, Micelli Ferrari T.

Introduction: Optical coherence tomography angiography (OCTA) could be a valid tool to detect choroidal neovascularization (CNV) in neovascular age-related macular degeneration (nAMD), allowing the analysis of the type, the morphology, and the extension of CNV in most of the cases.
Purpose: To determine the sensitivity and specificity of OCTA in detecting CNV secondary to nAMD, compared to fluorescein angiography (FA) and indocyanine green angiography (ICGA).

Methods: Prospective observational study. Patients with suspected nAMD were recruited between May and December 2016. Patients underwent FA, ICGA, spectral domain OCT, and OCTA (AngioVue, Optovue, Inc.). Sensitivity and specificity of FA, with or without ICGA, were assessed and compared with OCTA.

Results: Seventy eyes of 70 consecutive patients were included: 32 eyes (45.7%) with type I CNV, 8 eyes (11.4%) with type II CNV, 4 eyes (5.7%) with type III CNV, 6 eyes (8.6%) with mixed type I and type II CNV, and 20 eyes (28.6%) with no CNV. Sensitivity of OCTA was 88% and specificity was 90%. Concordance between FA/ICGA and OCTA was very good (0.91; range 0.81-1.00).

Conclusions: OCTA showed high sensitivity and specificity for detection of CNV. Concordance between OCTA and gold-standard dye-based techniques was excellent. OCTA may represent a first-line noninvasive method for the diagnosis of nAMD.

PMID: 29707575 PMCID: PMC5863302 DOI: 10.1155/2018/6724818


Impact of drusen and drusenoid retinal pigment epithelium elevation size and structure on the integrity of the retinal pigment epithelium layer.

Ferdinand S, Baumann B, Sacu S, Baumann L, Pircher M, Hitzenberger CK, Schmidt-Erfurth UM.

Purpose: To evaluate the impact of drusen size and structure on retinal pigment epithelium (RPE) and photoreceptor layers in eyes with early to intermediate age-related macular degeneration (AMD) using polarisation-sensitive optical coherence tomography (OCT).

Design: Retrospective investigation of an observational cross-sectional study.

Participants: Patients with early to intermediate AMD.

Methods: Twenty-five eyes of 25 patients with drusen were imaged with polarisation-sensitive OCT using macular volume scans. Each scan was manually graded for six distinct drusen characteristics and the integrity of both the overlying RPE and photoreceptor layer. The central scan of each single druse, as well as its diameter and location, were selected for statistical calculations.

Results: A total number of 5933 individual drusen including their adjacent RPE and photoreceptor layer were evaluated. 41.3% of all drusen demonstrated an intact overlying RPE; in 28.1% the RPE layer was irregular, but continuous. In 30.6%, the RPE layer signal was discontinuous above the area of drusen. The level of RPE alteration was significantly related to shape (p<0.001), internal reflectivity (p<0.001) and homogeneity (p<0.001) of the drusen and their diameter, with a higher probability for larger drusen to have a discontinuous RPE (OR 3.2, p<0.001). The number of drusen showing overlying foci or an altered photoreceptor layer was too small to be conclusive, but showed a trend towards an altered RPE if present.

Conclusions: Polarisation-sensitive OCT reveals a correlation between specific drusen characteristics and the integrity of the overlying RPE layer. Drusen diameter and configuration were significantly associated with RPE loss.

PMID: 29706603 DOI: 10.1136/bjophthalmol-2017-311782
Pathogenesis


Polarized Exosome Release from the Retinal Pigmented Epithelium.

Klingeborn M, Stamer WD, Bowes Rickman C.

Abstract: The retinal pigmented epithelium (RPE) forms the outer blood-retinal barrier and provides nutrients and recycling of visual pigment to the photoreceptors, among many other functions. The RPE is also a key site of pathophysiological changes in age-related macular degeneration, making it an important focus of study in both visual health and disease. Exosomes are nanometer-sized vesicles that are released by cells in a controlled fashion and mediate a range of extra- and intercellular activities. Some key exosome actions include cell-cell communication, immune modulation, extracellular matrix turnover, stem cell division/differentiation, neovascularization, and cellular waste removal. While much is known about their role in cancer and cardiovascular disease, exosome function in the many specialized tissues of the eye is just beginning to undergo rigorous study. Here we review current knowledge of the functions and roles of exosomes and other small extracellular vesicles released from the RPE. In particular, we discuss the potential role and importance of polarized exosome release from the RPE.

PMID: 29721985 DOI: 10.1007/978-3-319-75402-4_65


VEGF as a Trophic Factor for Müller Glia in Hypoxic Retinal Diseases.

Fu S, Dong S, Zhu M, Le YZ.

Abstract: Age-related macular degeneration (AMD) and diabetic retinopathy (DR), leading causes of blindness, share a common retinal environment: hypoxia which is a major stimulator for the upregulation of vascular endothelial growth factor (VEGF), a cardinal pathogenic factor for the breakdown of blood-retina barrier (BRB). As a result of intensive studies on VEGF pathobiology, anti-VEGF strategy has become a major therapeutics for wet AMD and DR. To investigate the potential impact of anti-VEGF strategy on major retinal supporting cells, Müller glia (MG), we disrupted VEGF receptor-2 (VEGFR2) in MG with conditional knockout (CKO) and examined the effect of VEGFR2-null on MG viability and neuronal integrity in mice. VEGFR2 CKO mice demonstrated a significant loss of MG density in diabetes/hypoxia, which in turn resulted in accelerated retinal degeneration. These defects appear similar to the clinical characteristics in a significant portion of wet-AMD patients with long-term anti-VEGF therapies. In this article, we will discuss the potential relevance of these clinical characteristics to the critical role of VEGF signaling in MG viability and neuronal integrity in hypoxia.

PMID: 29721978 DOI: 10.1007/978-3-319-75402-4_58


Pigment Epithelium-derived Factor Protects Retinal Pigment Epithelial Cells Against Cytotoxicity "In Vitro".

Nadal-Nicolas FM, Becerra SP.

Abstract: Oxidative stress has been implicated in neurodegenerative diseases, such as age-related macular degeneration. Hydrogen peroxide and sodium iodate can mediate oxidative injury. Sodium iodate induces a selective retinal degeneration targeting the RPE. We describe a method of chronic sodium iodate-mediated injury on RPE cells that may serve to evaluate protective factors against oxidative stress. Cytotoxicity and cell viability curves of ARPE-19 cells with sodium iodate were generated. The antioxidant pigment...
epithelium-derived factor decreased sodium iodate-mediated cytotoxicity without affecting ARPE-19 cell viability. A cell culture system to evaluate protection against oxidative stress injury with PEDF is discussed.

PMID: 29721976 DOI: 10.1007/978-3-319-75402-4_56


The Role of Microbiota in Retinal Disease.

Rowan S, Taylor A.

Abstract: The ten years since the first publications on the human microbiome project have brought enormous attention and insight into the role of the human microbiome in health and disease. Connections between populations of microbiota and ocular disease are now being established, and increased accessibility to microbiome research and insights into other diseases is expected to yield enormous information in the coming years. With the characterization of the ocular microbiome, important insights have already been made regarding corneal and conjunctival tissues. Roles for non-ocular microbiomes in complex retinal diseases are now being evaluated. For example, the gut microbiome has been implicated in the pathogenesis of uveitis. This short review will summarize the few studies linking gut or oral microbiota to diabetic retinopathy (DR), glaucoma, and age-related macular degeneration (AMD). We will also conjecture where the most significant findings still remain to be elucidated. Finally, we will propose the gut-retina axis, related but distinct from the gut-brain axis.

PMID: 29721973 DOI: 10.1007/978-3-319-75402-4_53


Bisretinoid Photodegradation Is Likely Not a Good Thing.

Ueda K, Kim HJ, Zhao J, Sparrow JR.

Abstract: Retinaldehyde adducts (bisretinoids) accumulate in retinal pigment epithelial (RPE) cells as lipofuscin. Bisretinoids are implicated in some inherited and age-related forms of macular degeneration that lead to the death of RPE cells and diminished vision. By comparing albino and black-eyed mice and by rearing mice in darkness and in cyclic light, evidence indicates that bisretinoid fluorophores undergo photodegradation in the eye (Ueda et al. Proc Natl Acad Sci 113:6904-6909, 2016). Given that the photodegradation products modify and impair cellular and extracellular molecules, these processes likely impart cumulative damage to retina.

PMID: 29721969 DOI: 10.1007/978-3-319-75402-4_49


The Role of c-Jun N-Terminal Kinase (JNK) in Retinal Degeneration and Vision Loss.

Kim BJ, Zack DJ.

Abstract: c-Jun N-terminal kinase (JNK), a member of stress-induced mitogen-activated protein (MAP) kinase family, has been shown to modulate a variety of biological processes associated with neurodegenerative pathology of the retina. In particular, various retinal cell culture and animal models related to glaucoma, age-related macular degeneration (AMD), and retinitis pigmentosa indicate that JNK signaling may contribute to disease pathogenesis. This mini-review discusses the impact of JNK signaling in retinal disease, with a focus on retinal ganglion cells (RGCs), photoreceptor cells, retinal pigment
epithelial (RPE) cells, and animal studies, with particular attention to modulation of JNK signaling as a potential therapeutic target for the treatment of retinal disease.

PMID: 29721963 DOI: 10.1007/978-3-319-75402-4_43


Early Endosome Morphology in Health and Disease.

Kaur G, Lakkaraju A.

Abstract: Early endosomes are organelles that receive macromolecules and solutes from the extracellular environment. The major function of early endosomes is to sort these cargos into recycling and degradative compartments of the cell. Degradation of the cargo involves maturation of early endosomes into late endosomes, which, after acquisition of hydrolytic enzymes, form lysosomes. Endosome maturation involves recruitment of specific proteins and lipids to the early endosomal membrane, which drives changes in endosome morphology. Defects in early endosome maturation are generally accompanied by alterations in morphology, such as increase in volume and/or number. Enlarged early endosomes have been observed in Alzheimer's disease and Niemann Pick Disease type C, which also exhibit defects in endocytic sorting. This article discusses the mechanisms that regulate early endosome morphology and highlights the potential importance of endosome maturation in the retinal pigment epithelium.

PMID: 29721961 DOI: 10.1007/978-3-319-75402-4_41


Role of Fibulins 2 and 5 in Retinal Development and Maintenance.

Ikelle L, Naash MI, Al-Ubaidi MR.

Abstract: Fibulins 2 and 5 are part of a seven-member family of proteins integral to the retinal extracellular matrix. Our study aimed to further explore the roles of both fibulins in retinal function. We obtained knockout mouse models of both fibulins and performed immunohistochemistry, electroretinography, and histology to investigate the outcome of eliminating these proteins. Immunohistochemical analysis showed that both fibulins are localized to the RPE, choroid, and Bruch's membrane. Functional testing showed a significantly reduced scotopic A response at 1 month of age, when compared to their wild-type counterpart. This functional reduction remained constant throughout the age of the animal and only declined as a result of normal aging. The functional decline was associated with reduced number of photoreceptor cells. The results presented clearly demonstrate that fibulins 2 and 5, as extracellular proteins, are necessary for normal retinal development.

PMID: 29721953 DOI: 10.1007/978-3-319-75402-4_33


Pleiotropic Effects of Risk Factors in Age-Related Macular Degeneration and Seemingly Unrelated Complex Diseases.

Kiel C, Weber BHF, Grassmann F.

Abstract: Age-related macular degeneration (AMD) is a complex disease with both environmental and genetic factors influencing disease risk. Genome-wide case-control association studies, candidate gene analyses, and epidemiological studies reinforced the notion that AMD is predominantly a disease of an impaired complemet system and an altered high-density lipoprotein (HDL) metabolism. Recent reports
demonstrated the pleiotropic role of the complement system and HDL in complex diseases such as cardiovascular disease, autoimmune disorders, cancer, and Alzheimer's disease. In light of these findings, we explore current evidence for a shared genetic and environmental risk of AMD and unrelated complex diseases based on epidemiological studies. Shared risk factors may indicate common pathways in disease pathology and thus may have implications for novel treatment options of AMD pathology.

PMID: 29721950 DOI: 10.1007/978-3-319-75402-4_30


Neuroinflammation in Retinitis Pigmentosa, Diabetic Retinopathy, and Age-Related Macular Degeneration: A Minireview.

Massengill MT, Ahmed CM, Lewin AS, Ildefonso CJ.

Abstract: The eye is an immuno-privileged organ. However, certain diseases such as uveitis are intrinsically linked to inflammation. In several retinal degenerative diseases, there is a unique damage at the onset of the disease, but evidence suggests that chronic and low-grade inflammatory processes play an important role in their progression. Studies have identified similar signaling pathways and changes in resident immune cells within the retina among these diseases. Herein, we will discuss some of these studies and propose how understanding this inflammatory response could aid in the development of therapies.

PMID: 29721943 DOI: 10.1007/978-3-319-75402-4_23


The Role of Hypoxia, Hypoxia-Inducible Factor (HIF), and VEGF in Retinal Angiomatous Proliferation.

Barben M, Samardzija M, Grimm C.

Abstract: In industrialized countries, age-related macular degeneration (AMD) is the leading cause of blindness in elderly people. Hallmarks of the non-neovascular (dry) form of AMD are the formation of drusen and geographic atrophy, whereas the exudative (wet) form of the disease is characterized by invading blood vessels. In retinal angiomatous proliferation (RAP), a special form of wet AMD, intraretinal vessels grow from the deep plexus into the subretinal space. Little is known about the mechanisms leading to intraretinal neovascularization, but age-related changes such as reduction of choroidal blood flow, accumulation of drusen, and thickening of the Bruch's membrane may lead to reduced oxygen availability in photoreceptors. Such a chronic hypoxic situation may induce several cellular response pathways including the stabilization of hypoxia-inducible factors (HIFs) and the production of angiogenic factors, such as vascular endothelial growth factor (VEGF). Here, we discuss the potential contribution of hypoxia and HIFs in RAP disease pathology and in some mouse models for subretinal neovascularization.

PMID: 29721942 DOI: 10.1007/978-3-319-75402-4_22


Anaphylatoxin Signaling in Retinal Pigment and Choroidal Endothelial Cells: Characteristics and Relevance to Age-Related Macular Degeneration.

Rohrer B.

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness in the USA. Polymorphisms in various complement components are associated with an increased risk for AMD, and it
has been hypothesized that an overactive complement system is partially responsible for the pathology of AMD. AMD is classified as early, intermediate, or late AMD, depending on the degree of the associated pathologies. Late AMD can be characterized as either lesions associated with neovascular AMD or geographic atrophy. Both sets of lesions are associated with pathology at the RPE/choroid interface, which include a thickening of Bruch's membrane, presence of drusen, and pigmentary alterations, and deterioration of the blood-retina barrier has been reported. These changes can lead to the slow degeneration and atrophy of the photoreceptors in the macula in dry AMD, or progress to choroidal neovascularization (CNV) and leakage of these new vessels in wet AMD. It has been shown previously that complement anaphylatoxins C3a and C5a, signaling via their respective G-protein-coupled receptors, can alter RPE cell function and promote choroidal neovascularization. However, it is important to note these components also play a role in tissue repair. Here we discuss anaphylatoxin signaling in AMD-related target cells and the potential implications for the design of anti-complement therapeutics.

PMID: 29721926 DOI: 10.1007/978-3-319-75402-4_6


Alterations in Extracellular Matrix/Bruch’s Membrane Can Cause the Activation of the Alternative Complement Pathway via Tick-Over.

Fernandez-Godino R.

Abstract: Given the complex etiology of age-related macular degeneration (AMD), treatments are developed to target intermediate/late stages of the disease. Unfortunately, the design of therapies for early stages of the disease is limited by our understanding of the mechanisms involved in the formation of basal deposits and drusen, the first clinical signs of AMD. During the last decade, the identification of common and rare alleles in complement genes as risk AMD variants in addition to the presence of active complement components in basal deposits and drusen has provided compelling evidence that the complement system plays a key role in the pathobiology of AMD. However, the mechanisms for complement activation in AMD are unknown. Here we propose that the activation of the complement system is a consequence of alterations in the aged extracellular matrix (ECM) of the retinal pigment epithelium (RPE)/Bruch's membrane (BrM), which favors the anchoring of complement C3b generated by convertase-independent cleavage of C3 via tick-over and produces a chronic activation of the alternative complement pathway.

PMID: 29721924 DOI: 10.1007/978-3-319-75402-4_4


Toll-Like Receptors and Age-Related Macular Degeneration.

Mulfaul K, Rhatigan M, Doyle S.

Abstract: Age-related macular degeneration (AMD) is the leading cause of central vision loss in the over 50s worldwide. Activation of the immune system has been implicated in disease progression, but while polymorphisms in genes associated with the immune system have been identified as risk factors for disease, the underlying pathways and mechanisms involved in disease progression remain incompletely characterised. Typically inflammatory responses are mediated by microbial infection; however, in chronic conditions, a form of 'sterile’ inflammation exists whereby immune responses occur in areas of the body, in the absence of microbes; ‘sterile’ inflammation is likely to be central to AMD. In this case the innate immune response is triggered when alarm signals released by stressed cells or damaged tissue are identified by pattern recognition receptors (PRRs). Toll-like receptors (TLRs) are a family of membrane-spanning PRRs for which host-derived ligands have been identified; these include heat shock proteins, extracellular matrix breakdown products, mRNA from necrotic cells and modified lipids. Here we review the evidence for TLR
Mitochondria: Potential Targets for Protection in Age-Related Macular Degeneration.

Brown EE, Lewin AS, Ash JD.

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness in older adults in developed countries. The molecular mechanisms of disease pathogenesis remain poorly understood; however, evidence suggests that mitochondrial dysfunction may contribute to the progression of the disease. Studies have shown that mitochondrial DNA lesions are increased in the retinal pigment epithelium (RPE) of human patients with the disease and that the number of these lesions increases with disease severity. Additionally, microscopy of human RPE from patients with dry AMD shows severe disruptions in mitochondrial inner and outer membrane structure, mitochondrial size, and mitochondrial cellular organization. Thus, improving our understanding of mitochondrial dysfunction in dry AMD pathogenesis may lead to the development of targeted therapies. We propose that mitochondrial dysfunction in the RPE can lead to the chronic oxidative stress associated with the disease. Therefore, one protective strategy may involve the use of small molecule therapies that target the regulation of mitochondrial biogenesis and mitochondrial fission and mitophagy.

Oxidative Stress Regulation and DJ-1 Function in the Retinal Pigment Epithelium: Implications for AMD.

Bonilha VL.

Abstract: In the retina, oxidative stress can initiate a cascade of events that ultimately leads to a focal loss of RPE cells and photoreceptors, a major contributing factor in geographic atrophy. Despite these implications, the molecular regulation of RPE oxidative metabolism under physiological and pathological conditions remains largely unknown. DJ-1 functions as an antioxidant, redox-sensitive molecular chaperone, and transcription regulator, which protected cells from oxidative stress. Here we discuss our progress toward characterization of the DJ-1 function in the protection of RPE to oxidative stress.

New concepts in macrophage ontogeny in the adult neural retina.

Saban DR.

Abstract: The number of neurons dedicated to vision itself is thought to be greater than the sum of the four other senses combined. Yet, little attention has been payed to the retina as compared to elsewhere in the central nervous system with respect to microglia, the macrophages of the neural parenchyma. Indeed, major advancements in the understanding of microglial ontogeny and maintenance in brain and spinal cord are now widely appreciated, whereas less notice has been given to the neural retina in this regard. The current Review covers topical concepts on adult microglia and perivascular macrophage ontogenies in the steady state retina, as well as parallels made with these macrophages in other areas of the central nervous system.
system. The subject of recruited monocytes and their descendant monocyte-derived macrophages in degenerative diseases of the retina is also integrated into this Review. Key experiments that have led to the theories covered are highlighted throughout, as are the knowledge gaps that remain unresolved.

PMID: 29703455 DOI: 10.1016/j.cellimm.2018.04.008

**Genetics and gene therapy**


**MicroRNA as Therapeutics for Age-Related Macular Degeneration.**

Natoli R, Fernando N.

**Abstract:** MicroRNA (miRNA) are a class of endogenously expressed small non-coding RNA molecules that function by repressing or silencing post-transcriptional gene expression. While miRNAs were only identified in humans as recently as the turn of this century, some miRNA-based agents are already in Phase 2 clinical trials (Christopher et al. 2016). This rapid progress from initial discovery to drug development reflects the effectiveness of miRNAs as therapeutic targets. Further, their use as therapeutic agents in the treatment of diseases such as Alzheimer's disease (Wang et al. 2014) supports their use in other neurodegenerative diseases, such as Age-Related Macular Degeneration (AMD). However, despite ∼300 miRNAs reportedly expressed in the human retina (Xu 2009), relatively little research has been conducted into the therapeutic potential of miRNAs for the treatment of AMD. This review will investigate the use of miRNAs as therapeutic and diagnostic molecules for AMD.

PMID: 29721925 DOI: 10.1007/978-3-319-75402-4_5


**Whole-Exome Sequencing in Age-Related Macular Degeneration Identifies Rare Variants in COL8A1, a Component of Bruch's Membrane.**

Corominas J, Colijn JM, Geerlings MJ et al

**Purpose:** Genome-wide association studies and targeted sequencing studies of candidate genes have identified common and rare variants that are associated with age-related macular degeneration (AMD). Whole-exome sequencing (WES) studies allow a more comprehensive analysis of rare coding variants across all genes of the genome and will contribute to a better understanding of the underlying disease mechanisms. To date, the number of WES studies in AMD case-control cohorts remains scarce and sample sizes are limited. To scrutinize the role of rare protein-altering variants in AMD cause, we performed the largest WES study in AMD to date in a large European cohort consisting of 1125 AMD patients and 1361 control participants.

**Design:** Genome-wide case-control association study of WES data.

**Participants:** One thousand one hundred twenty-five AMD patients and 1361 control participants.

**Methods:** A single variant association test of WES data was performed to detect variants that are associated individually with AMD. The cumulative effect of multiple rare variants with 1 gene was analyzed using a gene-based CMC burden test. Immunohistochemistry was performed to determine the localization of the Col8a1 protein in mouse eyes.

**Main Outcome Measures:** Genetic variants associated with AMD.

**Results:** We detected significantly more rare protein-altering variants in the COL8A1 gene in patients with AMD.
(22/2250 alleles [1.0%]) than in control participants (11/2722 alleles [0.4%]; P = 7.07×10-5). The association of rare variants in the COL8A1 gene is independent of the common intergenic variant (rs140647181) near the COL8A1 gene previously associated with AMD. We demonstrated that the Col8a1 protein localizes at Bruch's membrane.

Conclusions: This study supported a role for protein-altering variants in the COL8A1 gene in AMD pathogenesis. We demonstrated the presence of Col8a1 in Bruch's membrane, further supporting the role of COL8A1 variants in AMD pathogenesis. Protein-altering variants in COL8A1 may alter the integrity of Bruch's membrane, contributing to the accumulation of drusen and the development of AMD.

PMID: 29706360 DOI: 10.1016/j.opth.2018.03.040

Stem cells


Stem Cell-Based RPE Therapy for Retinal Diseases: Engineering 3D Tissues Amenable for Regenerative Medicine.

Ben M'Barek K, Habeler W, Monville C.

Abstract: Recent clinical trials based on human pluripotent stem cell-derived retinal pigment epithelium cells (hPSC-RPE cells) were clearly a success regarding safety outcomes. However the delivery strategy of a cell suspension, while being a smart implementation of a cell therapy, might not be sufficient to achieve the best results. More complex reconstructed tissue formulations are required, both to improve functionality and to target pathological conditions with altered Bruch's membrane like age-related macular degeneration (AMD). Herein, we describe the various options regarding the stem cell source choices and the different strategies elaborated in the recent years to develop engineered RPE sheets amenable for regenerative therapies.

PMID: 29721996 DOI: 10.1007/978-3-319-75402-4_76

Case Report

Rinsho Shinkeigaku. 2018 Apr 28. [Epub ahead of print] [Article in Japanese]

[Embolic stroke immediately after initial administration of intravitreal aflibercept].

Mizutani H, Inatomi Y, Singu T, Nakajima M, Yonehara T, Ando Y.

Abstract: A 72-year-old man was admitted to our hospital because of right upper limb monoplegia 8 hours after the initial intravitreal injection of aflibercept, which is an inhibitor of vascular endothelial growth factor. Magnetic resonance diffusion-weighted images showed recent ischemic lesions in the left corona radiata and the right superior frontal gyrus. Laboratory findings showed mild hyperfibrinolysis. A patent foramen ovale was diagnosed on transesophageal echocardiography; however, lower-extremity ultrasonography did not detect deep vein thrombosis. The source of embolism remained unknown. A possible mechanism of cerebral emboli in the present case was a rapidly induced hypercoagulative state due to transfer of aflibercept from the vitreous body to the systemic circulation.

PMID: 29710026 DOI: 10.5692/clinicalneurol.cn-001162

Disclaimer: This newsletter is provided as a free service to eye care professionals by the Macular Disease Foundation Australia. The Macular Disease 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.