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Drug treatment

Drugs Aging. 2011 Oct 3. [Epub ahead of print]

Therapeutic Efficacy of Bevacizumab for Age-Related Macular Degeneration: What are the Implications of CATT for Routine Management?

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Abstract

CATT (Comparison of Age-related macular degeneration [AMD] Treatment Trials) examined the efficacy of ranibizumab and bevacizumab for the treatment of neovascular AMD. This prospective, randomized, but unblinded trial revealed a significant improvement in vision with both treatments in terms of visual acuity; importantly, patients with juxtafoveal choroidal neovascularization (CNV) and retinal pigment epithelial detachments were not excluded from the study. Monthly treatment with the drugs resulted in similar increases in visual acuity, although angiograms indicated that ranibizumab was superior in terms of reducing retinal fluid and leakage. As the study also differentiated between a fixed regimen and an as-needed (pro re nata [PRN]) dosing regimen, a larger sample size and Bonferroni statistical correction were necessary. The equivalence of the PRN dosing of bevacizumab to the monthly treatment could not be confirmed. Almost all of the frequent deviations from the protocol (referring to retreatment criteria: 25.7-28.5%) resulted in under-treatment. Since this applied to both drugs equally, under-treatment alone could not explain the larger loss of visual acuity observed in the bevacizumab PRN arm. The PRN regimen was generally associated with a larger lesion size after 12 months compared with the fixed treatment regimens. The investigators accepted the drawbacks of an incomplete masking to allow co-payment by Medicare. As assessments of drug trials are often politically motivated, the higher demands of a non-inferiority trial compared with a superiority design must be emphasized. A comparison of the per-protocol and last-observation-carried-forward analysis has not yet been published; ongoing subgroup analysis might highlight the impact of different lesion characteristics. While CATT provided further evidence for the efficacy of bevacizumab treatment, differences in adverse events between the two treatments (e.g. a higher rate of serious adverse events with bevacizumab compared with ranibizumab) were reported; however, these still have to be analysed, with the larger sample sizes of previous ranibizumab studies needing to be taken into account. Preclinical studies imply some differences between the drugs in terms of their adverse event profiles. A possible increased risk of adverse events could not be ruled out by previous clinical case series and CATT because the sample sizes and the follow-up intervals were not adequate. The large discrepancy in the price of bevacizumab versus ranibizumab in the US means a cost-benefit analysis is warranted. A lack of quality-of-life data has prevented calculation of an appropriate bevacizumab price in the context of its performance in the ophthalmological set-

ting. Thus, CATT suggests that a favourable visual acuity might be achieved by very frequent administration of bevacizumab in patients with neovascular AMD. Although there are certain safety caveats, increased focus on subgroup analyses and obtaining longer follow-up data are expected to yield additional information of clinical relevance.

PMID: 21970950 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2011 Oct;152(4):509-14.

How the Comparison of Age-related Macular Degeneration Treatments Trial Results Will Impact Clinical Care.

Davis J, Olsen TW, Stewart M, Sternberg P Jr.

Bascom Palmer Eye Institute, Miami, Florida.

PURPOSE: To provide a perspective on the impact of the Comparison of Age-related Macular Degeneration Treatments Trial (CATT) on future clinical practices.

DESIGN: Interpretation of trial outcomes relative to clinical use of neovascular age-related macular degeneration (AMD) treatments, assessment of the influence of study design and execution on results, and review of unanalyzed safety data in the online supplement.

METHODS: Expert opinion.

RESULTS: The CATT study supports the selection of either ranibizumab or bevacizumab for treatment of AMD based on factors other than efficacy, such as cost, because monthly administration of bevacizumab was noninferior to the reference treatment of monthly ranibizumab in improving visual acuity at 1 year. Visual acuity results for bevacizumab as needed were inconclusive for noninferiority relative to monthly administration of either drug. The secondary outcome of decrease in thickness at the foveal center as measured by time-domain optical coherence tomography significantly favored the monthly ranibizumab group vs the bevacizumab-as-needed group but is more difficult to interpret as it did not correlate with visual acuity and is less appropriate for a noninferiority design. Bevacizumab groups had a statistically higher observed risk of serious adverse events; however, scrutiny of the online supplements shows similar numbers of cardiac and neurologic events in bevacizumab and ranibizumab users. Information regarding fellow eye treatment with anti-VEGF agents was not given.

CONCLUSIONS: CATT provides the first level I evidence for bevacizumab in a large number of patients with neovascular AMD. The trial supports use of either drug as primary therapy and suggests that modification of monthly dosing regimens is feasible. A difference in cardiovascular safety between the 2 drugs was not apparent on inspection of the supplementary safety data.

PMID: 21961847 [PubMed - in process]

Exp Eye Res. 2011 Sep 28. [Epub ahead of print]

Comparison of choroidal and retinal endothelial cells: Characteristics and response to VEGF isoforms and anti-VEGF treatments.

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Abstract

Neovascular eye diseases such as wet age-related macular degeneration and proliferative diabetic retinopathy are two of the most common causes of irreversible visual loss. Although mediated by vascular endothelial growth factor (VEGF), the mechanisms of these diseases are not fully understood. Molecular inhibitors of VEGF including pegaptanib, ranibizumab and bevacizumab are used as treatments for these diseases. However, there have been very few direct comparisons between these agents, and as dose and treatment regimes differ their relative efficacies are hard to determine. In vitro comparisons tend to use cells from different sites or species, which show heterogeneity in their responses. The aim of this study was to compare the characteristics of primary cultures of isolated human choroidal endothelial cells (hCEC) and retinal endothelial cells (hREC), and their proliferation responses to stimulation with VEGF 121 and 165, and to compare the anti-proliferative effects of these three drugs. hCEC and hREC were positive for the cell markers VEGFR1, VEGFR2, CD31, CD34 and von Willebrand's factor (vWF), with greater expression of CD34 on the hREC compared to hCEC. Contrary to previous assumptions VEGF isoforms 121 and 165 were found to be equally potent in stimulating endothelial cell proliferation. However, hREC exhibited higher proliferation with either VEGF isoform compared to hCEC. The anti-VEGF treatments ranibizumab and bevacizumab were effective in decreasing proliferation of hCEC induced by the two VEGF isoforms, individually and in combination, with ranibizumab being moderately more effective, particularly in hREC. Pegaptanib was effective in controlling the proliferation of hCEC stimulated by VEGF 165, but was ineffective against the stimulatory effect of VEGF 121. There were found to be significant differences in microvascular endothelial cells from the retina and choroid, both in the expression of cell markers and their behaviour in response to growth factors and currently available anti-VEGF agents, highlighting the importance of targeting treatments to specific intraocular vascular beds and/or diseases.

PMID: 21970900 [PubMed - as supplied by publisher]

Indian J Pharm Sci. 2010 Nov;72(6):675-88.

Nano-vectors for the Ocular Delivery of Nucleic Acid-based Therapeutics.

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Abstract

Nucleic acid-based therapeutics have gained a lot of interest for the treatment of diverse ophthalmic pathologies. The first to enter in clinic has been an oligonucleotide, Vitravene® for the treatment of cytomegalovirus infection. More recently, research on aptamers for the treatment of age related macular degeneration has led to the development of Macugen®. Despite intense potential, effective ocular delivery of nucleic acids is a major challenge since therapeutic targets for nucleic acid-based drugs are mainly located in the posterior eye segment, requiring repeated invasive administration. Of late, nanotechnology-based nano-vectors have been developed in order to overcome the drawbacks of viral and other non-viral vectors. The diversity of nano-vectors allows for ease of use, flexibility in application, low-cost of production, higher transfection efficiency and enhanced genomic safety. Using nano-vector strategies, nucleic acids can be delivered either encapsulated or complexed with cationic lipids, polymers or peptides forming sustained release systems, which can be tailored according to the ocular tissue being targeted. The present review focuses on developments and advances in various nano-vectors for the ocular delivery of nucleic acid-based therapeutics, the barriers that such delivery systems face and methods to overcome them.

PMID: 21969738 [PubMed - in process] PMCID: PMC3178967

Clin Ophthalmol. 2011;5:1303-8. Epub 2011 Sep 14.

Ranibizumab in the treatment of patients with visual impairment due to diabetic macular edema.

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Abstract

Diabetic macular edema is the major cause of visual acuity impairment in diabetic patients. The exact etiopathogenesis is unknown and, currently, grid/focal retinal laser photocoagulation represents the recommended treatment. It has been demonstrated that vascular endothelial growth factor (VEGF) plays a key role in the pathogenesis of diabetic macular edema by mediating vascular permeability and accumulation of intracellular and extracellular fluid, and thereby represents an appealing candidate as a therapeutic target for the treatment of diabetic macular edema. The advent of intravitreal anti-VEGF drugs has opened up a new era for the management of diabetic macular edema. At present, three anti-VEGF substances are available for routine clinical use, ie, pegaptanib, ranibizumab, and bevacizumab. The aim of this review is to summarize the evidence supporting the use of ranibizumab in clinical practice. Most of the studies analyzed in this review are prospective, controlled clinical trials that have focused on documenting the therapeutic effect of ranibizumab and its safety, providing encouraging results.

PMID: 21966206 [PubMed - in process] PMCID: PMC3180503

Graefes Arch Clin Exp Ophthalmol. 2011 Oct 2. [Epub ahead of print]

Anatomic response of occult choroidal neovascularization to intravitreal ranibizumab: a study by indocyanine green angiography.

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BACKGROUND: To investigate changes in indocyanine green angiography (ICGA) features of occult choroidal neovascularization (CNV) after intravitreal ranibizumab injections.

METHODS: We reviewed the charts of all consecutive patients with newly diagnosed occult CNV secondary to age-related macular degeneration (AMD) treated by intravitreal ranibizumab. In all patients, optical coherence tomography (OCT) and ICGA were performed at baseline, after 3 months and 12 months.

RESULTS: Fifty-one eyes of 44 patients (ten males, 34 females, mean age 77.8 ± 7.3 years) were included. Mean follow-up was 20.3 ± 6.2 months. During the first 12 months, patients received 5.5 ± 2.7 intravitreal ranibizumab injections. When compared with baseline, best-corrected visual acuity (BCVA) significantly improved at the 3-month follow-up visit (60.5 ± 22.0 vs 50.9 ± 20.7 letters, $p = 0.04$), and stabilized at 12-month visit (55.7 ± 18.2 letters; $p = 0.05$). Central macular thickness (CMT) significantly improved during follow-up ($229.0 \pm 54.7 \mu\text{m}$ vs $281.0 \pm 61.3 \mu\text{m}$ at baseline, $p = 0.003$). An overall stabilization was observed on ICGA in both the lesion area ($5.27 \pm 3.9 \text{ mm}^2$ at baseline vs $4.60 \pm 3.5 \text{ mm}^2$ at month 12, $p = 0.4$), and greatest linear dimension (GLD $2.66 \pm 1.2 \text{ mm}$ at baseline vs $2.55 \pm 1.0 \text{ mm}$ at month 12, $p = 0.3$). Eight eyes (15.7%) showed CNV growth on ICGA (lesion area $3.98 \pm 3.2 \text{ mm}^2$ at baseline vs $4.3 \pm 2.7 \text{ mm}^2$ at month-12, $p = 0.6$; GLD $2.11 \pm 1.0 \text{ mm}$ at baseline vs $2.70 \pm 0.8 \text{ mm}$ at month-12, $p = 0.05$).

CONCLUSION: ICGA suggests that functional outcomes after intravitreal ranibizumab is related to CMT reduction rather than CNV regression.

PMID: 21964851 [PubMed - as supplied by publisher]

Other treatment & diagnosis

J Ophthalmol. 2011;2011:764183. Epub 2011 Sep 29.

High-resolution optical coherence tomography retinal imaging: a case series illustrating potential and limitations.

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Purpose: To present a series of retinal disease cases that were imaged by spectral domain optical coherence tomography (SD-OCT) in order to illustrate the potential and limitations of this new imaging modality.

Methods: The series comprised four selected cases (one case each) of age-related macular degeneration (ARMD), diabetic retinopathy (DR), central retinal artery occlusion (CRAO), and branch retinal vein occlusion (BRVO). Patients were imaged using the Heidelberg Spectralis (Heidelberg Engineering, Germany) in SD-OCT mode. Patients also underwent digital fundus photography and clinical assessment.

Results: SD-OCT imaging of a case of age-related macular degeneration revealed a subfoveal choroidal neovascular membrane with detachment of the retinal pigment epithelium (RPE) and neurosensory retina. Using SD-OCT, the cases of DR and BRVO both exhibited macular edema with cystoid spaces visible in the outer retina.

Conclusions: The ability of SD-OCT to clearly and objectively elucidate subtle morphological changes within the retinal layers provides information that can be used to formulate diagnoses with greater confidence.

PMID: 21969910 [PubMed - in process] PMCID: PMC3182576

Pathogenesis

Nature. 2011 Oct 5;478(7367):76-81. doi: 10.1038/nature10449.

Complement factor H binds malondialdehyde epitopes and protects from oxidative stress.

Weismann D, Hartvigsen K, Lauer N, Bennett KL, Scholl HP, Charbel Issa P, Cano M, Brandstätter H, Tsimikas S, Skerka C, Superti-Furga G, Handa JT, Zipfel PF, Witztum JL, Binder CJ.

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Abstract

Oxidative stress and enhanced lipid peroxidation are linked to many chronic inflammatory diseases, including age-related macular degeneration (AMD). AMD is the leading cause of blindness in Western societies, but its aetiology remains largely unknown. Malondialdehyde (MDA) is a common lipid peroxidation product that accumulates in many pathophysiological processes, including AMD. Here we identify complement factor H (CFH) as a major MDA-binding protein that can block both the uptake of MDA-modified proteins by macrophages and MDA-induced proinflammatory effects in vivo in mice. The CFH polymorphism H402, which is strongly associated with AMD, markedly reduces the ability of CFH to bind MDA, indicating a causal link to disease aetiology. Our findings provide important mechanistic insights into innate immune responses to oxidative stress, which may be exploited in the prevention of and therapy for AMD and other chronic inflammatory diseases.

Comment in Nature. 2011;478(7367):42-3.

PMID: 21979047 [PubMed - in process]

Curr Eye Res. 2011 Oct 6. [Epub ahead of print]

Mitochondrial Dysfunction in Retinal Diseases.

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Abstract

The mitochondrion is a vital intracellular organelle for retinal cell function and survival. There is growing confirmation to support an association between mitochondrial dysfunction and a number of retinal degenerations. Investigations have also unveiled mitochondrial genomic instability as one of the contributing factors for age-related retinal pathophysiology. This review highlights the role of mitochondrial dysfunction originating from oxidative stress in the etiology of retinal diseases including diabetic retinopathy, glaucoma and age-related macular degeneration (AMD). Moreover, mitochondrial DNA (mtDNA) damage associated with AMD due to susceptibility of mtDNA to oxidative damage and failure of mtDNA repair pathways is also highlighted in this review. The susceptibility of neural retina and retinal pigment epithelium (RPE) mitochondria to oxidative damage with ageing appears to be a major factor in retinal degeneration. It thus appears that the mitochondrion is a weak link in the antioxidant defenses of retinal cells. In addition, failure of mtDNA repair pathways can also specifically contribute towards pathogenesis of AMD. This review will further summarize the prospective role of mitochondria targeting therapeutic agents for the treatment of retinal disease. Mitochondria based drug targeting to diminish oxidative stress or promote repair of mtDNA damage may offer potential alternatives for the treatment of various retinal degenerative diseases.

PMID: 21978133 [PubMed - as supplied by publisher]

Curr Eye Res. 2011 Oct 6. [Epub ahead of print]

Increased Expression of Tight Junctions in ARPE-19 Cells Under Endoplasmic Reticulum Stress.

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Purpose: To investigate the effects of endoplasmic reticulum (ER) stress on the tight junctions of the retinal pigment epithelial (RPE) cells in vitro.

Materials and Methods: ER stress was induced in cultured ARPE-19 cells, a human RPE cell line, by exposure to tunicamycin (TM) or to thapsigargin (TG). After 6, 12, 24 and 48 hours of exposure, the expressions of GRP78/Bip (Bip), C/EBP-homologous protein (CHOP), vascular endothelial growth factor (VEGF), zonula occludens (ZO)-1, occludin and claudin-1 were determined by real-time RT-PCR. Immunoblot analysis and/or immunohistochemistry for proteins of tight junctions and ER stress markers, viz., Bip, activating transcription factor (ATF) 6, CHOP, and caspase-4, were performed at 48 hours after the exposure. Enzyme-linked immunosorbent assay was used to determine the concentration of VEGF165. Transepithelial electrical resistance (TER) of the ARPE-19 cells was determined to measure the permeability.

Results: The expressions of the mRNAs and/or proteins of Bip, CHOP, ATF6 and caspase-4 were significantly increased in ARPE-19 cells under ER stress induced by TM and TG. The mRNAs of VEGF were also increased by both TM and TG. However, the concentration of VEGF165 was not significantly increased after 48 hours exposure to TM and TG compared to that of the control in the apical chamber medium. The proteins and mRNAs of occludin and claudin-1 were significantly increased by TM and TG, and that of ZO-1 was significantly increased by TG. Immunohistochemistry showed that the staining of ZO-1, occludin and claudin-1 under ER stress was stronger than that of the control. A significant increase of TER was observed after exposure to TM and TG.

Conclusions: The increased expressions of tight junction molecules by TM- or TG-exposed ARPE-19 cells indicate that ER stress can alter the function of RPE cells and may be involved in the pathogenesis of age-related macular degeneration.

PMID: 21978097 [PubMed - as supplied by publisher]

PLoS One. 2011;6(9):e24793. Epub 2011 Sep 28.

Synergistic inhibition of endothelial cell proliferation, tube formation, and sprouting by cyclosporin a and itraconazole.

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Abstract

Pathological angiogenesis contributes to a number of diseases including cancer and macular degeneration. Although angiogenesis inhibitors are available in the clinic, their efficacy against most cancers is modest due in part to the existence of alternative and compensatory signaling pathways. Given that angiogenesis is dependent on multiple growth factors and a broad signaling network in vivo, we sought to explore the potential of multidrug cocktails for angiogenesis inhibition. We have screened 741 clinical drug combinations for the synergistic inhibition of endothelial cell proliferation. We focused specifically on existing clinical drugs since the re-purposing of clinical drugs allows for a more rapid and cost effective transition to clinical studies when compared to new drug entities. Our screen identified cyclosporin A (CsA), an immunosuppressant, and itraconazole, an antifungal drug, as a synergistic pair of inhibitors of endothelial cell proliferation. In combination, the IC(50) dose of each drug is reduced by 3 to 9 fold. We also tested the ability of the combination to inhibit endothelial cell tube formation and sprouting, which are dependent on two essential processes in angiogenesis, endothelial cell migration and differentiation. We found that CsA and itraconazole synergistically inhibit tube network size and sprout formation. Lastly, we tested the combination on human foreskin fibroblast viability as well as Jurkat T cell and HeLa cell proliferation, and found that endothelial cells are selectively targeted. Thus, it is possible to combine existing clinical drugs to synergistically inhibit in vitro models of angiogenesis. This strategy may be useful in pursuing the next generation of antiangiogenesis therapy.

PMID: 21969860 [PubMed - in process] PMCID: PMC3182171

Proc Natl Acad Sci U S A. 2011 Oct 3. [Epub ahead of print]

Cell culture model that mimics drusen formation and triggers complement activation associated with age-related macular degeneration.

Johnson LV, Forest DL, Banna CD, Radeke CM, Maloney MA, Hu J, Spencer CN, Walker AM, Tsie MS, Bok D, Radeke MJ, Anderson DH.

Center for the Study of Macular Degeneration, Neuroscience Research Institute, University of California, Santa Barbara, CA 93106.

Abstract

We introduce a human retinal pigmented epithelial (RPE) cell-culture model that mimics several key aspects of early stage age-related macular degeneration (AMD). These include accumulation of sub-RPE deposits that contain molecular constituents of human drusen, and activation of complement leading to formation of deposit-associated terminal complement complexes. Abundant sub-RPE deposits that are rich in

apolipoprotein E (APOE), a prominent drusen constituent, are formed by RPE cells grown on porous supports. Exposure to human serum results in selective, deposit-associated accumulation of additional known drusen components, including vitronectin, clusterin, and serum amyloid P, thus suggesting that specific protein-protein interactions contribute to the accretion of plasma proteins during drusen formation. Serum exposure also leads to complement activation, as evidenced by the generation of C5b-9 immunoreactive terminal complement complexes in association with APOE-containing deposits. Ultrastructural analyses reveal two morphologically distinct forms of deposits: One consisting of membrane-bounded multivesicular material, and the other of nonmembrane-bounded particle conglomerates. Collectively, these results suggest that drusen formation involves the accumulation of sub-RPE material rich in APOE, a prominent biosynthetic product of the RPE, which interacts with a select group of drusen-associated plasma proteins. Activation of the complement cascade appears to be mediated via the classical pathway by the binding of C1q to ligands in APOE-rich deposits, triggering direct activation of complement by C1q, deposition of terminal complement complexes and inflammatory sequelae. This model system will facilitate the analysis of molecular and cellular aspects of AMD pathogenesis, and the testing of new therapeutic agents for its treatment.

PMID: 21969589 [PubMed - as supplied by publisher]

Biochem Biophys Res Commun. 2011 Sep 24. [Epub ahead of print]

Rapamycin sensitive mTOR activation mediates nerve growth factor (NGF) induced cell migration and pro-survival effects against hydrogen peroxide in retinal pigment epithelial cells.

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Abstract

Patients with age related macular degeneration (AMD) have a loss of vision in the center of the visual field. Oxidative stress plays an important role in this progress. Nerve growth factor (NGF) is important for the survival and maintenance of sympathetic and sensory neurons and NGF eye drops improve visual acuity and electro-functional activity in patients with AMD. However, the molecular mechanisms and signaling events involved in this have not been fully investigated. Using cultured human retinal pigment epithelial (RPE) cells, we demonstrate here that NGF protects RPE cells against hydrogen peroxide (H₂O₂)-induced cell apoptosis. NGF also induces RPE cell migration, the latter is important for retinal regeneration and the recovery from AMD. H₂O₂ decreases S6 phosphorylation and cell viability, which is restored by NGF. Rapamycin, the pharmacologic inhibitor of mammalian target of rapamycin (mTOR), diminished NGF-induced S6 phosphorylation, cell migration and protective effects against oxidative stress. Collectively, we conclude that activation of rapamycin sensitive mTOR signaling mediates NGF induced cell migration and pro-survival effects in H₂O₂ treated RPE cells.

PMID: 21968016 [PubMed - as supplied by publisher]

Aging Cell. 2011 Oct 3. doi: 10.1111/j.1474-9726.2011.00752.x. [Epub ahead of print]

Glycation-altered proteolysis as a pathobiologic mechanism that links dietary glycemic index, aging, and age-related disease (in non diabetics).

Uchiki T, Weikel KA, Jiao W, Shang F, Caceres A, Pawlak D, Handa JT, Brownlee M, Nagaraj R, Taylor A.

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MD Department of Medicine, Albert Einstein College of Medicine, Forchheimer Building, Room 531, 1300 Morris Park Av, Bronx, NY 10461 Department of Ophthalmology and Visual Sciences, Case Western Reserve University, Cleveland, OH 44106.

Abstract

Epidemiologic studies indicate that the risks for major age-related debilities including CHD, diabetes, and age-related macular degeneration (AMD) are diminished in people who consume lower glycemic index (GI) diets but lack of a unifying physiobiochemical mechanism that explains the salutary effect is a barrier to implementing dietary practices that capture the benefits of consuming lower GI diets. We established a simple murine model of age-related retinal lesions that precede AMD (hereafter called AMD-like lesions). We found that consuming a higher GI diet promotes these AMD-like lesions. However, mice that consumed the lower vs. higher GI diet had significantly reduced frequency ($p < 0.02$) and severity ($p < 0.05$) of hallmark age-related retinal lesions such as basal deposits. Consuming higher GI diets was associated with >3 fold higher accumulation of advanced glycation end products (AGEs) in retina, lens, liver and brain in the age-matched mice, suggesting diet-induced systemic glycative stress that is etiologic for lesions. Data from live cell and cell free systems show that the ubiquitin-proteasome system (UPS) and lysosome/autophagy pathway (LPS) are involved in the degradation of AGEs. Glycatively-modified substrates were degraded significantly slower than unmodified substrates by the UPS. Compounding the detriments of glycative stress, AGE-modification of ubiquitin and ubiquitin conjugating enzymes impaired UPS activities. Furthermore, ubiquitin conjugates and AGEs accumulate and are found in lysosomes when cells are glycatively stressed or the UPS or LPS/autophagy are inhibited indicating that the UPS and LPS interact with one another to degrade AGEs. Together these data explain why AGEs accumulate as glycative stress increases. © 2011 The Authors Aging Cell© 2011 Blackwell Publishing Ltd/Anatomical Society of Great Britain and Ireland.

PMID: 21967227 [PubMed - as supplied by publisher]

Essays Biochem. 2011 Sep 7;50(1):265-90.

Lipid transport by mammalian ABC proteins.

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Abstract

ABC (ATP-binding cassette) proteins actively transport a wide variety of substrates, including peptides, amino acids, sugars, metals, drugs, vitamins and lipids, across extracellular and intracellular membranes. Of the 49 human ABC proteins, a significant number are known to mediate the extrusion of lipids from membranes or the flipping of membrane lipids across the bilayer to generate and maintain membrane lipid asymmetry. Typical lipid substrates include phospholipids, sterols, sphingolipids, bile acids and related lipid conjugates. Members of the ABCA subfamily of ABC transporters and other ABC proteins such as ABCB4, ABCG1 and ABCG5/8 implicated in lipid transport play important roles in diverse biological processes such as cell signalling, membrane lipid asymmetry, removal of potentially toxic compounds and metabolites, and apoptosis. The importance of these ABC lipid transporters in cell physiology is evident from the finding that mutations in the genes encoding many of these proteins are responsible for severe inherited diseases. For example, mutations in ABCA1 cause Tangier disease associated with defective efflux of cholesterol and phosphatidylcholine from the plasma membrane to the lipid acceptor protein apoA1 (apolipoprotein AI), mutations in ABCA3 cause neonatal surfactant deficiency associated with a loss in secretion of the lipid pulmonary surfactants from lungs of newborns, mutations in ABCA4 cause Stargardt macular degeneration, a retinal degenerative disease linked to the reduced clearance of retinoid compounds from photoreceptor cells, mutations in ABCA12 cause harlequin and lamellar ichthyosis, skin diseases associated with defective lipid trafficking in keratinocytes, and mutations in ABCB4 and ABCG5/ABCG8 are responsible for pro-

gressive intrafamilial hepatic disease and sitosterolaemia associated with defective phospholipid and sterol transport respectively. This chapter highlights the involvement of various mammalian ABC transporters in lipid transport in the context of their role in cell signalling, cellular homeostasis, apoptosis and inherited disorders.

PMID: 21967062 [PubMed - in process]

Biochem Biophys Res Commun. 2011 Sep 21. [Epub ahead of print]

Phosphorylation/inactivation of PTEN by Akt-independent PI3K signaling in retinal pigment epithelium.

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Abstract

Retinal pigment epithelium (RPE) plays a critical role in vertebrate vision by providing functional and structural support to the retina. Degeneration of RPE by cumulative oxidative stresses or acute injury frequently results in retinal degenerative diseases, notably age-related macular degeneration (AMD). Moreover, it has been shown that phosphorylation-mediated inactivation of PTEN (phosphatase and tensin homolog) in RPE is closely linked to AMD-like retinal degeneration in mice [1]. In this study, we used AMD mouse models, in which chemokine (C-C motif) ligand 2 (Ccl2) or chemokine (C-C motif) receptor 2 (Ccr2) were genetically ablated, to examine mechanisms linking reactive oxygen species (ROS) to phosphorylation/inactivation of PTEN in RPE. We found that ROS levels were increased in these RPE cells in association with phosphorylation/inactivation of PTEN. Both PTEN phosphorylation/inactivation and consequent Akt activation in the RPE of AMD model mice were inhibited by antioxidant treatment, indicating a functional role for elevated intracellular ROS. We further discovered that PTEN phosphorylation in oxidatively stressed RPE was repressed by a phosphoinositide 3-kinase (PI3K) inhibitor, but not by an Akt inhibitor. Taken together, these results suggest that ROS-activated PI3K potentiates AMD-related RPE pathogenesis through phosphorylation/inactivation of PTEN.

PMID: 21964287 [PubMed - as supplied by publisher]

Epidemiology

Graefes Arch Clin Exp Ophthalmol. 2011 Oct 5. [Epub ahead of print]

Association of dilated retinal arteriolar caliber with early age-related macular degeneration: the Handan Eye Study.

Yang K, Zhan SY, Liang YB, Duan X, Wang F, Wong TY, Sun LP, Wang NL.

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BACKGROUND: To identify factors associated with early age-related macular degeneration (AMD) in a rural Chinese population, with emphasis on retinal vessel caliber.

METHODS: The study population comprised the 6,830 participants of the Handan Eye Study. All participants underwent digital retinal photography of both eyes. Trained graders assessed the presence of AMD

lesions. Arteriolar and venular diameters were measured with a specific computer-assisted program and were summarized as the central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE).

RESULTS: The data for the 199 individuals with evaluable retinal photographs and early AMD and 400 age-matched individuals randomly selected from the group without AMD were analyzed. After adjusting for participants' age, sex, smoking status, hypertension, diabetes, BMI, and CRVE, the multivariate adjusted model showed that a higher CRAE was significantly associated with early AMD (OR = 1.34; 95% CI: 1.05-1.71; $p = 0.020$) and the presence of soft distinct drusen (OR = 1.32 (95% CI: 1.02-1.71, $p = 0.037$). There were no significant associations between CRVE and early AMD.

CONCLUSIONS: Dilated retinal arteriolar caliber is associated with early AMD and soft distinct drusen in this population. We found no significant associations between CRAE and other characteristics of the retina related to AMD or between retinal venal caliber and early AMD. More research is needed to determine whether the difference between these results and those previously published stem from the rural living conditions of the participants or other factors.

PMID: 21971892 [PubMed - as supplied by publisher]

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