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Drug treatment

Retina. 2015 Jul 31. [Epub ahead of print]

VITREOMACULAR TRACTION AFFECTS ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR TREATMENT OUTCOMES FOR EXUDATIVE AGE-RELATED MACULAR DEGENERATION.

Krishnan R, Arora R, De Salvo G, Stinghe A, Severn PS, Pal B, Goverdhan S.

PURPOSE: To evaluate the effect of vitreomacular traction (VMT) on visual acuity outcomes and central retinal thickness (CRT) measurements after intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy for treatment of exudative age-related macular degeneration (AMD).

METHODS: In this retrospective series, the authors evaluate the clinical records and optical coherence tomography of 34 eyes of 32 patients, with VMT confirmed on optical coherence tomography at baseline, to assess the effects of VMT on anti-VEGF therapy for newly diagnosed exudative wet AMD. Best-corrected visual acuity at baseline, 1, 3, 6, 9, and 12 months and CRT at baseline, 3, 6, and 12 months were assessed. Comparison was made with a control group of 29 eyes of 28 patients with wet AMD and no VMT on optical coherence tomography and with key variable-dosing studies for anti-VEGF in exudative AMD (CATT, HARBOR, PrONTO, SUSTAIN, and Gupta et al).

RESULTS: Best-corrected visual acuity results showed a visual acuity improvement that peaked at 3 months with 2.47 letters, well below other variable-dosing studies for anti-VEGF therapy in exudative AMD. This was then followed by a steady decline with mean best-corrected visual acuity at 12 months ending below the baseline level (-1.00 letters) compared with a gain of 9.39 letters in the control group at 12 months. Comparison of the mean CRT in the VMT group between baseline and 12 months showed no significant difference ($P = 0.67$), whereas the PrONTO study and control groups showed a highly significant difference at 12 months compared with baseline ($P < 0.001$). Mean CRT values at 6 months and 12 months were essentially at baseline levels ($0.26 \mu\text{m}$, $-0.62 \mu\text{m}$, respectively).

CONCLUSION: Vitreomacular traction at baseline, existing concurrently with newly diagnosed exudative AMD treated with intravitreal anti-VEGF therapy on a variable-dosing regime, was associated with poorer visual outcomes and a decreased response to reduction in CRT, compared with a control group of wet AMD without VMT and compared with major variable-dosing studies for intravitreal anti-VEGF in exudative AMD.

PMID: 26237240 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2015 Aug 1;56(9):5040-7.

Baseline Predictors for Good Versus Poor Visual Outcomes in the Treatment of Neovascular Age-Related Macular Degeneration With Intravitreal Anti-VEGF Therapy.

Chae B, Jung JJ, Mrejen S, Gallego-Pinazo R, Yannuzzi NA, Patel SN, Chen CY, Marsiglia M, Boddu S, Freund KB.

PURPOSE: To examine the baseline factors associated with good (20/60 or better) versus poor (20/200 or worse) visual outcomes in eyes with treatment-naïve neovascular age-related macular degeneration (AMD) receiving intravitreal anti-vascular endothelial growth factor (VEGF) on a treat-and-extend regimen (TER).

METHODS: An observational, retrospective series of patients managed with a TER, identified as having either good or poor visual outcomes, was examined. A multivariate regression analysis of baseline characteristics identified factors associated with good and poor vision at 2, 3, and 4 years. Neovascular subtypes were identified using fluorescein angiography (FA) alone and the anatomic classification system with FA and optical coherence tomography (OCT).

RESULTS: One hundred thirty-eight patients (154 eyes) fit the inclusion criteria at 2 years, 106 patients (113 eyes) at 3 years, and 72 patients (74 eyes) at 4 years. In the multivariate analysis, type 1 lesions, according to anatomic classification, had better vision at 24 months (95% CI: [3.1, 82.7], $P = 0.01$), 36 months (95% CI: [1.97, 24.17], $P = 0.003$), and 48 months (95% CI: [2.01, 65.47], $P = 0.006$). Clopidogrel use was associated with poor vision at 24 months (95% CI: [0.03, 0.68], $P = 0.013$). Vision at 3 months was the best predictor of vision at year 4 ($\beta = -4.277$, $P = 0.002$).

CONCLUSIONS: Eyes with neovascular AMD managed with a TER of anti-VEGF therapy having type 1 neovascularization at baseline were more likely to maintain good vision over 4 years, whereas clopidogrel use predicted poor vision at 2 years. Vision at 3 months was the best predictor for favorable long-term vision.

PMID: 26237196 [PubMed - in process]

Drugs. 2015 Aug 5. [Epub ahead of print]

Diabetic Macular Edema: Options for Adjunct Therapy.

Calvo P, Abadia B, Ferreras A, Ruiz-Moreno O, Verdes G, Pablo LE.

Abstract: Diabetes mellitus (DM) is a chronic disease that affects 387 million people worldwide. Diabetic retinopathy (DR), a common complication of DM, is the main cause of blindness in the active population. Diabetic macular edema (DME) may occur at any stage of DR, and is characterized by vascular hyperpermeability accompanied by hard exudates within the macula. Medical and surgical therapies have dramatically reduced the progression of DR, and timely intervention can reduce the risk of severe vision loss by more than 90 %. In 2012, intravitreal ranibizumab became the first anti-vascular endothelial growth factor (anti-VEGF) agent approved for DME and, since then, many reports of the use of ranibizumab for DME have been promising. Randomized, prospective, multicenter clinical trials—most notably, RESOLVE, READ-2, RISE/RIDE, RESTORE, DRCR.net protocol I, and RETAIN—reported improvements in best-corrected visual acuity and decreased central retinal thickness as measured with optical coherence tomography in patients with DME. Similar treatment benefits have also been noted in clinical trials evaluating intravitreal aflibercept and bevacizumab (DAVINCI, VISTA/VIVID, and BOLT) and more recently DRCR.net protocol T. Intravitreal steroids (dexamethasone intravitreal implant and fluocinolone acetonide), particularly in refractory cases, also play a significant role in the management of DME (MEAD/CHAMPLAIN and FAMOUS/FAME studies). In summary, over the last 5 years, blocking VEGF and inflammation has been shown to improve visual outcomes in patients with macular edema due to DM, revolutionizing the treatment of center-involved DME and establishing a new standard of care.

PMID: 26242766 [PubMed - as supplied by publisher]

PLoS One. 2015 Aug 4;10(8):e0135050. eCollection 2015.

Comparison of Outcomes and Costs of Ranibizumab and Aflibercept Treatment in Real-Life.

Schmid MK, Reich O, Faes L, Boehni SC, Bittner M, Howell JP, Thiel MA, Signorell A, Bachmann LM.

BACKGROUND: Treatment efficacy and costs of anti-VEGF drugs have not been studied in clinical routine.

OBJECTIVE: To compare treatment costs and clinical outcomes of the medications when adjusting for patients' characteristics and clinical status.

DESIGN: Comparative study.

SETTING: The largest public ophthalmologic clinic in Switzerland.

PATIENTS: Health care claims data of patients with age-related macular degeneration, diabetic macula edema and retinal vein occlusion were matched to clinical and outcome data.

MEASUREMENTS: Patients' underlying condition, gender, age, visual acuity and retinal thickness at baseline and after completing the loading phase, the total number of injections per treatment, the visual outcome and vital status was secured.

RESULTS: We included 315 patients (19595 claims) with a follow-up time of 1 to 99 months (mean 32.7, SD 25.8) covering the years 2006-2014. Mean age was 78 years (SD 9.3) and 200 (63.5%) were female. At baseline, the mean number of letters was 55.6 (SD 16.3) and the central retinal thickness was 400.1 μ m (SD 110.1). Patients received a mean number of 15.1 injections (SD 13.7; range 1 to 85). Compared to AMD, adjusted cost per month were significantly higher (+2174.88 CHF, 95%CI: 1094.50-3255.27; $p < 0.001$) for patients with DME, while cost per month for RVO were slightly but not significantly higher. (+284.71 CHF, 95% CI: -866.73-1436.15; $p = 0.627$).

CONCLUSIONS: Patients with DME are almost twice as expensive as AMD and RVO patients. Cost excess occurs with non-ophthalmologic interventions. The currently licensed anti-VEGF medications did not differ in costs, injection frequency and clinical outcomes. Linking health care claims to clinical data is a useful tool to examine routine clinical care.

PMID: 26241852 [PubMed - in process] PMCID: PMC4524713

J Clin Med. 2015 Jul 8;4(7):1380-402.

Long-Term Visual Outcomes for a Treat and Extend Anti-Vascular Endothelial Growth Factor Regimen in Eyes with Neovascular Age-Related Macular Degeneration.

Mrejen S, Jung JJ, Chen C, Patel SN, Gallego-Pinazo R, Yannuzzi N, Xu L, Marsiglia M, Boddu S, Freund KB.

Abstract: With the advent of anti-vascular endothelial growth factor (VEGF) therapy, clinicians are now focused on various treatment strategies to better control neovascular age-related macular degeneration (NVAMD), a leading cause of irreversible blindness. Herein, we retrospectively reviewed consecutive patients with treatment-naïve NVAMD initially classified based on fluorescein angiography (FA) alone or with an anatomic classification utilizing both FA and optical coherence tomography (OCT) and correlated long-term visual outcomes of these patients treated with an anti-VEGF Treat-and-Extend Regimen (TER) with baseline characteristics including neovascular phenotype. Overall, 185 patients (210 eyes) were followed over an average of 3.5 years (range 1-6.6) with a retention rate of 62.9%, and visual acuity significantly improved with a TER that required a mean number of 8.3 (± 1.6) ($\pm$ standard deviation) intravitreal anti-VEGF injections/year (range 4-13). The number of injections and the anatomic classification were independent predictors of visual acuity at 6 months, 1, 2, 3 and 4 years. Patients with Type 1 neovascularization had better visual outcomes and received more injections than the other neovascular subtypes. There were no serious adverse events. A TER provided sustained long-term visual gains. Eyes

with Type 1 neovascularization had better visual outcomes than those with other neovascular subtypes.

PMID: 26239682 [PubMed] PMCID: PMC4519796

J Clin Med. 2015 May 21;4(5):1079-101.

Individualized Treatment of Neovascular Age-Related Macular Degeneration: What are Patients Gaining? Or Losing?

Stewart MW.

Abstract: The widespread use of drugs that bind diffusible vascular endothelial growth factor (VEGF) has revolutionized the treatment of neovascular age-related macular degeneration (AMD). The pivotal ranibizumab and aflibercept registration trials featured monthly intravitreal injections for 12 months, during which visual acuities and macular edema rapidly improved for the first 3 months and modest gains or stabilization continued until the primary endpoint. In many subsequent trials, patients were evaluated monthly and treated as-needed (PRN) according to the results of visual acuity (VA) testing, fundus examinations and optical coherence tomography scans. Compared to monthly-treated control groups, PRN treated patients require fewer injections during the first year but they also experience smaller VA gains (1-3 letters). A small number of prospective trials that directly compared monthly with PRN therapy showed that VA gains with discontinuous therapy lag slightly behind those achieved with monthly injections. Physicians recognize that monthly office visits with frequent intraocular injections challenge patients' compliance, accrue high drug and professional service costs, and clog office schedules with frequently returning patients. To decrease the numbers of both office visits and anti-VEGF injections without sacrificing VA gains, physicians have embraced the treat-and-extend strategy. Treat-and-extend has not been studied as rigorously as PRN but it has become popular among both vitreoretinal specialists and patients. Despite the possible risks associated with discontinuous therapy (decreased VA and increased macular fluid), most physicians individualize treatment (PRN or treat-and-extend) for the majority of their patients. This review chapter explores the many advantages of individualized therapy, while balancing these against suboptimal responses due to the decreased frequency of anti-VEGF injections.

PMID: 26239466 [PubMed] PMCID: PMC4470218

Korean J Ophthalmol. 2015 Aug;29(4):226-32. Epub 2015 Jul 21.

Aflibercept Treatment for Neovascular Age-related Macular Degeneration and Polypoidal Choroidal Vasculopathy Refractory to Anti-vascular Endothelial Growth Factor.

Moon da RC, Lee DK, Kim SH, You YS, Kwon OW.

PURPOSE: To report the results of switching treatment to vascular endothelial growth factor (VEGF) Trap-Eye (aflibercept) in neovascular age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV) refractory to anti-VEGF (ranibizumab and bevacizumab).

METHODS: This is a retrospective study involving 32 eyes from 29 patients; 18 were cases of neovascular AMD and 14 were cases of PCV. The best-corrected visual acuity (BCVA) and central macular thickness (CMT) of spectral-domain optical coherence tomography were evaluated.

RESULTS: BCVA and CMT improved from 0.58 to 0.55 ($p = 0.005$) and from 404 to 321 μm ($p < 0.001$), respectively, after switching to aflibercept. The 14 eyes that received 6 or more aflibercept injections remained stable at 0.81 to 0.81 and 321 to 327 μm ($p = 1.0, 0.29$), respectively, after 3 aflibercept injections. The 10 eyes that received 3 or more bevacizumab injections after 3 or more aflibercept injections worsened, from 0.44 to 0.47 and from 332 to 346 μm ($p = 0.06, 0.05$), respectively. The results showed similar improvement of BCVA and CMT in neovascular AMD and PCV.

CONCLUSIONS: Aflibercept seems to be effective for improvement and maintenance of BCVA and CMT

for neovascular AMD and PCV refractory to anti-VEGF. Switching from aflibercept back to bevacizumab treatment may not be a proper strategy.

PMID: 26240506 [PubMed - in process] PMCID: PMC4520865

Expert Rev Clin Pharmacol. 2015 Aug 7:1-8. [Epub ahead of print]

Conbercept (KH-902) for the treatment of neovascular age-related macular degeneration.

Nguyen TT, Guymer R.

Abstract: Age-related macular degeneration (AMD) is a progressive, degenerative disease of the retina that occurs with increasing incidence with age and ranks third among the global causes of visual impairment. VEGF has been implicated in the development and progression of neovascular AMD. Drugs that block VEGF, leading to regression of the abnormal blood vessels, are the mainstay of treatment of neovascular AMD, particularly for subfoveal neovascular lesions. Anti-VEGF agents currently in use in neovascular AMD are pegaptanib (Macugen®), ranibizumab (Lucentis®), bevacizumab (Avastin®) and a soluble VEGF receptor decoy aflibercept (Eylea®). Recently, China Food and Drug Administration have approved conbercept for the treatment of neovascular AMD in China. Conbercept appears to offer yet another anti-VEGF drug for use in neovascular AMD. However, there is still a need for large, well-designed, randomized clinical trials to ensure its safety and efficacy.

PMID: 26250840 [PubMed - as supplied by publisher]

Retin Cases Brief Rep. 2015 Jul 31. [Epub ahead of print]

RESOLUTION OF A GIANT PIGMENT EPITHELIAL DETACHMENT WITH HALF-DOSE AFLIBERCEPT.

Nagiel A, Sadda SR, Schwartz SD, Sarraf D.

PURPOSE: To describe the use of half-dose anti-vascular endothelial growth factor therapy in a patient with giant pigment epithelial detachments.

METHODS: Observational case report. A 76-year-old woman with neovascular age-related macular degeneration presented with massive bilateral pigment epithelial detachments measuring over 1000 µm in height. Her right eye was treated with standard-dose aflibercept, which led to two large retinal pigment epithelium tears. Treatment of the left eye with half-dose aflibercept led to complete resolution of the detachment without tear formation.

RESULTS: Half-dose anti-vascular endothelial growth factor therapy resulted in resolution of a giant pigment epithelial detachment ~1500 µm in maximal height and 10 mm in diameter.

CONCLUSION: Reduced-dose anti-vascular endothelial growth factor therapy may be considered as a treatment option for very large pigment epithelial detachments at high risk for retinal pigment epithelium tear formation.

PMID: 26237136 [PubMed - as supplied by publisher]

J Clin Med. 2015 Feb 12;4(2):343-59.

Age-Related Macular Degeneration: Advances in Management and Diagnosis.

Yonekawa Y, Miller JW, Kim IK.

Abstract: Age-related macular degeneration (AMD) is the most common cause of irreversible visual

impairment in older populations in industrialized nations. AMD is a late-onset deterioration of photoreceptors and retinal pigment epithelium in the central retina caused by various environmental and genetic factors. Great strides in our understanding of AMD pathogenesis have been made in the past several decades, which have translated into revolutionary therapeutic agents in recent years. In this review, we describe the clinical and pathologic features of AMD and present an overview of current diagnosis and treatment strategies.

PMID: 26239130 [PubMed] PMCID: PMC4470128

Other treatment & diagnosis

Ophthalmology. 2015 Aug 3. [Epub ahead of print]

Photopsias: A Key to Diagnosis.

Brown GC, Brown MM, Fischer DH.

PURPOSE: To assess the character and cause of photopsias in vitreoretinal patients.

DESIGN: Cross-sectional study.

PARTICIPANTS: A total of 169 consecutive patients (217 eyes) with vitreoretinal disease presenting with a history of photopsias.

METHODS: A total of 217 eyes with photopsias in 169 patients were evaluated. Photopsia assessment included (1) laterality (unilateral, bilateral but not simultaneous, bilateral, and simultaneous); (2) morphology (flash, zig-zag, strobe, scintillating scotoma, twinkling, other); (3) color (white, silver, yellow, combination, other); (4) location (temporal, central, other); (5) duration (quick, prolonged, constant, other); (6) frequency; (7) diurnal appearance (day, night, both); (8) stimuli (turning head or eyes, hypoglycemia, hyperglycemia, other); and (9) associated systemic or ocular signs and symptoms (headache, numbness, weakness, vertigo, syncope, diplopia, hypotension, floaters, other).

MAIN OUTCOME MEASURES: Clinical photopsia features correlated with the causes of photopsias.

RESULTS: Thirty-two photopsia causes were identified. The top 16 included posterior vitreous detachment (PVD) in 39.7% of eyes; retinal tear in 8.9% of eyes; neovascular age-related macular degeneration (AMD) in 7.9% of eyes; rhegmatogenous retinal detachment (RRD) in 7.5% of eyes; classic and ophthalmic migraine in 6.5% of eyes; hypoglycemia in 2.8% of eyes; vertebrobasilar insufficiency in 2.8% of eyes; non-AMD choroidal neovascularization in 2.3% of eyes; retinitis pigmentosa in 1.9% of eyes; severe cough in 1.9% of eyes; central serous chorioretinopathy in 1.4% of eyes; intraocular lens reflections in 0.9% of eyes; blue field entoptic phenomenon in 0.9% of eyes; Charles Bonnet syndrome in 0.9% of eyes; digitalis in 0.9% of eyes; and metastatic adenocarcinoma to the brain in 0.9% of eyes. The photopsias associated with PVD are typically quick (96%), with lightning/flash morphology (96%), white (87%), temporally located (86%), associated with new-onset floaters (85%), preferentially seen in dark (90%) rather than lighted environments (29%), and often initiated by head/eye movements (60%). Retinal detachment had a similar profile, but with more nontemporal photopsias (40%) ($P = 0.01$). The photopsias from neovascular AMD are more centrally located (83%), quick and repetitive (79%), seen in light (73%) and dark (63%) environments, have no inciting stimuli (84%), and are more likely to be nonwhite (40%).

CONCLUSIONS: A pointed history for photopsias can reveal a cause that may not initially seem apparent. Thus, the history can play a key role in management decisions.

PMID: 26249730 [PubMed - as supplied by publisher]

Ophthalmic Surg Lasers Imaging Retina. 2015 Jul 1;46(7):724-7.

Serous Index of Pigment Epithelial Detachments in Neovascular Age-Related Macular Degeneration Predicts Response to Anti-Vascular Endothelial Growth Factor Treatment.

Young M, Forooghian F.

BACKGROUND AND OBJECTIVE: To determine whether optical density measurements of pigment epithelial detachments (PEDs) in neovascular age-related macular degeneration (AMD) can predict the response to treatment with anti-VEGF therapy.

PATIENTS AND METHODS: Retrospective review of SD-OCT scans of 21 eyes of 21 patients with neovascular AMD and PED. Response to treatment was determined using SD-OCT volumetric analysis. The authors used optical density measurements of PED lesions on SD-OCT images to calculate the serous index, which is a measure of the serous component of PEDs.

RESULTS: The serous index was found to correlate with the response to anti-VEGF treatment ($r = .69$, $P = .0005$), and to be predictive of the response to treatment ($P = .007$).

CONCLUSION: The serous index of PEDs can help predict the response to anti-VEGF treatment. This measure may be useful in decisions regarding switching anti-VEGF agents in the clinical care of patients with neovascular AMD and PED. [Ophthalmic Surg Lasers Imaging Retina. 2015;46:724-727.].

PMID: 26247453 [PubMed - in process]

Ophthalmic Surg Lasers Imaging Retina. 2015 Jul 1;46(7):718-23.

Predictability of Recurrent Exudation and Subretinal Hemorrhaging in Neovascular Age-Related Macular Degeneration With Indocyanine Green Angiography.

Rush RB, Rush SW, Aragon AV 2nd, Ysasaga JE.

BACKGROUND AND OBJECTIVE: To report the predictability of recurrent exudation and subretinal hemorrhaging after treatment extension in neovascular age-related macular degeneration (AMD) through assessment of interval changes in choroidal neovascularization (CNV) size on indocyanine green (ICG) angiography.

PATIENTS AND METHODS: The charts of patients with neovascular AMD who underwent bevacizumab therapy using a treat-and-extend protocol were retrospectively reviewed over a 12-month period.

RESULTS: An increase of 33% or more in CNV surface area on ICG angiography from 4 to 6 weeks, 6 to 8 weeks, and 8 to 10 weeks was observed in patients whose treatment interval could not be extended from 6 to 8 weeks, 8 to 10 weeks, and 10 to 12 weeks, respectively, and this was significant compared to patients whose treatment interval was successfully extended during those respective intervals ($P < .0001$, $P = .0002$, $P = .0004$, respectively).

CONCLUSION: CNV size change on ICG angiography can predict which patients are likely to experience recurrent exudation and/or subretinal hemorrhaging after treatment extension using treat-and-extend bevacizumab. [Ophthalmic Surg Lasers Imaging Retina. 2015;46:718-723.].

PMID: 26247452 [PubMed - in process]

J Clin Med. 2015 Mar 31;4(4):567-78.

Patient-Specific iPSC-Derived RPE for Modeling of Retinal Diseases.

Nguyen HV, Li Y, Tsang SH.

Abstract: Inherited retinal diseases, such as age-related macular degeneration and retinitis pigmentosa, are the leading cause of blindness in the developed world. Currently, treatments for these conditions are limited. Recently, considerable attention has been given to the possibility of using patient-specific induced pluripotent stem cells (iPSCs) as a treatment for these conditions. iPSCs reprogrammed from adult somatic cells offer the possibility of generating patient-specific cell lines in vitro. In this review, we will discuss the current literature pertaining to iPSC modeling of retinal disease, gene therapy of iPSC-derived retinal pigmented epithelium (RPE) cells, and retinal transplantation. We will focus on the use of iPSCs created from patients with inherited eye diseases for testing the efficacy of gene or drug-based therapies, elucidating previously unknown mechanisms and pathways of disease, and as a source of autologous cells for cell replacement.

PMID: 26239347 [PubMed] PMCID: PMC4470156

Ophthalmology. 2015 Aug 4. [Epub ahead of print]

Impairments in Dark Adaptation Are Associated with Age-Related Macular Degeneration Severity and Reticular Pseudodrusen.

Flamendorf J, Agrón E, Wong WT, Thompson D, Wiley HE, Doss EL, Al-Holou S, Ferris FL 3rd, Chew EY, Cukras C.

PURPOSE: We investigate whether ocular and person-based characteristics were associated with dark adaptation (DA).

DESIGN: Cross-sectional, single-center, observational study.

PARTICIPANTS: One hundred sixteen participants older than 50 years of age with a range of age-related macular degeneration (AMD) severity.

METHODS: Participants underwent best-corrected visual acuity (BCVA) testing, ophthalmoscopic examination, and multimodal imaging. Presence of reticular pseudodrusen (RPD) was assessed by masked grading of fundus images and was confirmed with optical coherence tomography. Eyes also were graded for AMD features (drusen, pigmentary changes, late AMD) to generate person-based AMD severity groups. One eye was designated the study eye for DA testing. Nonparametric statistical testing was performed on all comparisons.

MAIN OUTCOME MEASURES: The primary outcome of this study was the rod intercept time (RIT), which is defined as the time for a participant's visual sensitivity to recover to a stimulus intensity of 5×10^{-3} cd/m² (a decrease of 3 log units), or until a maximum test duration of 40 minutes was reached.

RESULTS: A total of 116 study eyes from 116 participants (mean age, 75.4 ± 9.4 years; 58% female) were analyzed. Increased RIT was associated significantly with increasing AMD severity, increasing age ($r = 0.34$; $P = 0.0002$), decreasing BCVA ($r = -0.54$; $P < 0.0001$), pseudophakia ($P = 0.03$), and decreasing subfoveal choroidal thickness ($r = -0.27$; $P = 0.003$). Study eyes with RPD (15/116 [13%]) had a significantly greater mean RIT compared with eyes without RPD in any AMD severity group ($P < 0.02$ for all comparisons), with 80% reaching the DA test ceiling.

CONCLUSIONS: Impairments in DA increased with age, worse visual acuity, presence of RPD, AMD severity, and decreased subfoveal choroidal thickness. Analysis of covariance found the multivariate model that best fit the data included age, AMD group, and presence of RPD ($R^2 = 0.56$), with the presence of RPD conferring the largest parameter estimate.

PMID: 26253372 [PubMed - as supplied by publisher]

Brain Res. 2015 Jul 31. pii: S0006-8993(15)00584-3. doi: 10.1016/j.brainres.2015.06.053. [Epub ahead of print]

Regenerative cellular Therapies for neurologic Diseases.

Levy M, Boulis N, Rao M, Svendsen CN.

Abstract: The promise of stem cell regeneration has been the hope of many neurologic patients with permanent damage to the central nervous system. There are hundreds of stem cell trials worldwide intending to test the regenerative capacity of stem cells in various neurological conditions from Parkinson's disease to multiple sclerosis. Although no stem cell therapy is clinically approved for use in any human disease indication, patients are seeking out trials and asking clinicians for guidance. This review summarizes the current state of regenerative stem cell transplantation divided into seven conditions for which trials are currently active: demyelinating diseases/spinal cord injury, amyotrophic lateral sclerosis, stroke, Parkinson's disease, Huntington's disease, macular degeneration and peripheral nerve diseases.

PMID: 26239912 [PubMed - as supplied by publisher]

J Clin Med. 2015 Jan 29;4(2):282-303.

Tapping Stem Cells to Target AMD: Challenges and Prospects.

Brandl C, Grassmann F, Riolfi J, Weber BH.

Abstract: Human pluripotent stem cells (hPSCs) are increasingly gaining attention in biomedicine as valuable resources to establish patient-derived cell culture models of the cell type known to express the primary pathology. The idea of "a patient in a dish" aims at basic, but also clinical, applications with the promise to mimic individual genetic and metabolic complexities barely reflected in current invertebrate or vertebrate animal model systems. This may particularly be true for the inherited and complex diseases of the retina, as this tissue has anatomical and physiological aspects unique to the human eye. For example, the complex age-related macular degeneration (AMD), the leading cause of blindness in Western societies, can be attributed to a large number of genetic and individual factors with so far unclear modes of mutual interaction. Here, we review the current status and future prospects of utilizing hPSCs, specifically induced pluripotent stem cells (iPSCs), in basic and clinical AMD research, but also in assessing potential treatment options. We provide an outline of concepts for disease modelling and summarize ongoing and projected clinical trials for stem cell-based therapy in late-stage AMD.

PMID: 26239128 [PubMed] PMCID: PMC4470125

J Clin Med. 2014 Dec 19;3(4):1511-41.

iPS Cells for Modelling and Treatment of Retinal Diseases.

Chen FK, McLenachan S, Edel M, Da Cruz L, Coffey PJ, Mackey DA.

Abstract: For many decades, we have relied on immortalised retinal cell lines, histology of enucleated human eyes, animal models, clinical observation, genetic studies and human clinical trials to learn more about the pathogenesis of retinal diseases and explore treatment options. The recent availability of patient-specific induced pluripotent stem cells (iPSC) for deriving retinal lineages has added a powerful alternative tool for discovering new disease-causing mutations, studying genotype-phenotype relationships, performing therapeutics-toxicity screening and developing personalised cell therapy. This review article provides a clinical perspective on the current and potential benefits of iPSC for managing the most common blinding diseases of the eye: inherited retinal diseases and age-related macular degeneration.

PMID: 26237613 [PubMed] PMCID: PMC4470196

J Clin Med. 2014 Dec 29;4(1):37-65.

The Potential for iPS-Derived Stem Cells as a Therapeutic Strategy for Spinal Cord Injury: Opportunities and Challenges.

Khazaei M, Siddiqui AM, Fehlings MG.

Abstract: Spinal cord injury (SCI) is a devastating trauma causing long-lasting disability. Although advances have occurred in the last decade in the medical, surgical and rehabilitative treatments of SCI, the therapeutic approaches are still not ideal. The use of cell transplantation as a therapeutic strategy for the treatment of SCI is promising, particularly since it can target cell replacement, neuroprotection and regeneration. Cell therapies for treating SCI are limited due to several translational roadblocks, including ethical and practical concerns regarding cell sources. The use of iPSCs has been particularly attractive, since they avoid the ethical and moral concerns that surround other stem cells. Furthermore, various cell types with potential for application in the treatment of SCI can be created from autologous sources using iPSCs. For applications in SCI, the iPSCs can be differentiated into neural precursor cells, neurons, oligodendrocytes, astrocytes, neural crest cells and mesenchymal stromal cells that can act by replacing lost cells or providing environmental support. Some methods, such as direct reprogramming, are being investigated to reduce tumorigenicity and improve reprogramming efficiencies, which have been some of the issues surrounding the use of iPSCs clinically to date. Recently, iPSCs have entered clinical trials for use in age-related macular degeneration, further supporting their promise for translation in other conditions, including SCI.

PMID: 26237017 [PubMed] PMCID: PMC4470238

Pathogenesis

Neurobiol Aging. 2015 Jun 17. [Epub ahead of print]

Inhibition of aberrant complement activation by a dimer of acetylsalicylic acid.

Lee M, Wathier M, Love JA, McGeer E, McGeer PL.

Abstract: We here report synthesis for the first time of the acetyl salicylic acid dimer 5,5'-methylenebis(2-acetoxybenzoic acid) (DAS). DAS inhibits aberrant complement activation by selectively blocking factor D of the alternative complement pathway and C9 of the membrane attack complex. We have previously identified aurin tricarboxylic and its oligomers as promising agents in this regard. DAS is much more potent, inhibiting erythrocyte hemolysis by complement-activated serum with an IC₅₀ in the 100-170 nanomolar range. There are numerous conditions where self-damage from the complement system has been implicated in the pathology, including such chronic degenerative diseases of aging as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and age-related macular degeneration. Consequently, there is a high priority for the discovery and development of agents that can successfully treat such conditions. DAS holds considerable promise for being such an agent.

PMID: 26248865 [PubMed - as supplied by publisher]

BMB Rep. 2015 Aug 7. pii: 3286. [Epub ahead of print]

Wnt5a attenuates the pathogenic effects of the Wnt/ β -catenin pathway in human retinal pigment epithelial cells via down-regulating β -catenin and Snail.

Kim JH, Park S, Chung H, Oh S1.

Abstract: Activation of the Wnt/ β -catenin pathway plays a pathogenic role in age-related macular degeneration (AMD) and is thus a potential target for the development of therapeutics for this disease. Here, we demonstrated that Wnt5a antagonized β -catenin response transcription (CRT) induced with

Wnt3a by promoting β -catenin phosphorylation at Ser33/Ser37/Thr41 and its subsequent degradation in human retinal pigment epithelial (RPE) cells. Wnt5a decreased the levels of vascular endothelial growth factor (VEGF), tumor necrosis factor- α (TNF- α), and nuclear factor- κ B (NF- κ B), which was up-regulated by Wnt3a. Furthermore, Wnt5a increased E-cadherin expression and decreased cell migration by down-regulating Snail expression, thereby abrogating the Wnt3a-induced epithelial-mesenchymal transition (EMT) in human RPE cells. Our findings suggest that Wnt5a suppresses the pathogenic effects of canonical Wnt signaling in human RPE cells by promoting β -catenin phosphorylation and degradation. Therefore, Wnt5a has significant therapeutic potential for the treatment of AMD.

PMID: 26246285 [PubMed - as supplied by publisher]

J Clin Med. 2015 May 4;4(5):874-83.

Can Novel Treatment of Age-Related Macular Degeneration Be Developed by Better Understanding of Sorsby's Fundus Dystrophy.

Gourier HC, Chong NV.

Abstract: Sorsby's Fundus Dystrophy (SFD) is a rare autosomal dominant maculopathy that shares many clinical features with Age-Related Macular Degeneration (AMD). It is caused by a mutation in a single gene, TIMP-3, which accumulates in Bruch's membrane (BM). BM thickening and TIMP-3 accumulation can also be found in AMD. From our understanding of the pathophysiology of SFD we hypothesize that BM thickening could be responsible for making the elastic layer vulnerable to invasion by choriocapillaris, thereby leading to choroidal neovascularization in some cases of AMD, whilst in others it could deprive the retinal pigment epithelium of its blood supply, thereby causing geographic atrophy.

PMID: 26239453 [PubMed] PMCID: PMC4470204

J Clin Med. 2015 Jan 14;4(1):172-92.

NLRP3 Inflammasome and Pathobiology in AMD.

Celkova L, Doyle SL, Campbell M.

Abstract: Age-related macular degeneration (AMD) is the leading cause of central vision loss and blindness in the elderly. It is characterized by a progressive loss of photoreceptors in the macula due to damage to the retinal pigment epithelium (RPE). Clinically, it is manifested by drusen deposition between the RPE and underlying choroid and accumulation of lipofuscin in the RPE. End-stage disease is characterized by geographic atrophy (dry AMD) or choroidal neovascularization (wet AMD). The NLRP3 inflammasome has recently been implicated in the disease pathology. Here we review the current knowledge on the involvement of this multiprotein complex and its effector cytokines interleukin-1 β (IL-1 β) and IL-18 in AMD progression. We also describe cell death mechanisms that have been proposed to underlie RPE degeneration in AMD and discuss the role of autophagy in the regulation of disease progression.

PMID: 26237026 [PubMed] PMCID: PMC4470247

Neurobiol Aging. 2015 Sep;36(9):2637-48. Epub 2015 Jun 9.

Cd59a deficiency in mice leads to preferential innate immune activation in the retinal pigment epithelium-choroid with age.

Herrmann P, Cowing JA, Cristante E, Liyanage SE, Ribeiro J, Duran Y, Abelleira Hervas L, Carvalho LS, Bainbridge JW, Luhmann UF, Ali RR.

Abstract: Dysregulation of the complement system has been implicated in the pathogenesis of age-related

macular degeneration. To investigate consequences of altered complement regulation in the eye with age, we examined Cd59a complement regulator deficient (Cd59a^{-/-}) mice between 4 and 15 months. In vivo imaging revealed an increased age-related accumulation of autofluorescent spots in Cd59a^{-/-} mice, a feature that reflects accumulation of subretinal macrophages and/or microglia. Despite this activation of myeloid cells in the eye, Cd59a^{-/-} mice showed normal retinal histology and function as well as normal choroidal microvasculature. With age, they revealed increased expression of activators of the alternative complement pathway (C3, Cfb, Cfd), in particular in the retinal pigment epithelium (RPE)-choroid but less in the retina. This molecular response was not altered by moderately-enhanced light exposure. Cd59a deficiency therefore leads to a preferential age-related dysregulation of the complement system in the RPE-choroid, that alone or in combination with light as a trigger, is not sufficient to cause choroidal vascular changes or retinal degeneration and dysfunction. This data emphasizes the particular vulnerability of the RPE-choroidal complex to dysregulation of the alternative complement pathway during aging.

PMID: 26234657 [PubMed - in process]

J Clin Med. 2014 Nov 3;3(4):1234-57.

Age-Related Macular Degeneration: A Disease of Systemic or Local Complement Dysregulation?

Warwick A, Khandhadia S, Ennis S, Lotery A.

Abstract: Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in developed countries. The role of complement in the development of AMD is now well-established. While some studies show evidence of complement dysregulation within the eye, others have demonstrated elevated systemic complement activation in association with AMD. It is unclear which one is the primary driver of disease. This has important implications for designing novel complement-based AMD therapies. We present a summary of the current literature and suggest that intraocular rather than systemic modulation of complement may prove more effective.

PMID: 26237601 [PubMed] PMCID: PMC4470180

Epidemiology

J Clin Med. 2015 Apr 24;4(5):782-821.

Polypoidal Choroidal Vasculopathy in Asians.

Wong CW, Wong TY, Cheung CM.

Abstract: Age related macular degeneration (AMD) in Asians has been suggested to differ from their Western counterparts in terms of epidemiology, pathogenesis, clinical presentation and treatment. In particular, polypoidal choroidal vasculopathy (PCV) appears to be the predominant subtype of exudative AMD in Asian populations, in contrast to choroidal neovascularization secondary to AMD (CNV-AMD) in Western populations. Epidemiological data on PCV has been largely limited to hospital-based studies and there are currently no data on the incidence of PCV. Similarities and differences in risk factor profile between PCV and CNV-AMD point to some shared pathogenic mechanisms but also differential underlying mechanisms leading to the development of each phenotype. Serum biomarkers such as CRP, homocysteine and matrix metalloproteinases suggest underlying inflammation, atherosclerosis and deranged extracellular matrix metabolism as possible pathogenic mechanisms. In addition, recent advances in genome sequencing have revealed differences in genetic determinants of each subtype. While the standard of care for CNV-AMD is anti-vascular endothelial growth factor (VEGF) therapy, photodynamic therapy (PDT) has been the mainstay of treatment for PCV, although long-term visual prognosis remains unsatisfactory. The optimal treatment for PCV requires further clarification, particularly with different types of anti-VEGF agents and possible benefits of reduced fluence PDT.

PMID: 26239448 [PubMed] PMCID: PMC4470199

PLoS One. 2015 Aug 7;10(8):e0134338.

Association between Blood Lead Levels and Age-Related Macular Degeneration.

Hwang HS, Lee SB, Jee D.

PURPOSE: To investigate the association between blood lead levels and prevalence of age-related macular degeneration (AMD).

METHODS: A nationwide population-based cross-sectional study included 4,933 subjects aged over 40 years who participated in the 2008-2012 Korean National Health and Nutrition Examination Survey, and for whom fundus photographs were available. All participants underwent a standardized interview, evaluation of blood lead concentration, and a comprehensive ophthalmic examination. Digital fundus photographs (45°) were taken of both eyes under physiological mydriasis. All fundus photographs were graded using an international classification and grading system.

RESULTS: Mean blood lead levels were 3.15 µg/dL in men and 2.27 µg/dL in women ($P < 0.001$). After adjusting for potential confounders including age, gender, smoking status, total cholesterol levels, triglyceride levels, heart problems and strokes, the adjusted odds ratio (OR) in women for any AMD was 1.86 (95% Confidence Interval [CI], 1.03-3.36) and for early AMD was 1.92 (95% CI, 1.06-3.48), for those in the highest quintile of lead level compared with the lowest quintile. In men, however, blood lead level was not significantly associated with AMD.

CONCLUSIONS: Blood lead levels were higher in men, but were only associated with AMD in women. Increased levels of blood lead may be involved in the pathogenesis of AMD development in women.

PMID: 26252225 [PubMed - as supplied by publisher]

Genetics

Biomed Res Int. 2015;2015:524821. Epub 2015 Jul 5.

An Improved Opposition-Based Learning Particle Swarm Optimization for the Detection of SNP-SNP Interactions.

Shang J, Sun Y, Li S, Liu JX, Zheng CH, Zhang J.

Abstract: SNP-SNP interactions have been receiving increasing attention in understanding the mechanism underlying susceptibility to complex diseases. Though many works have been done for the detection of SNP-SNP interactions, the algorithmic development is still ongoing. In this study, an improved opposition-based learning particle swarm optimization (IOBLPSO) is proposed for the detection of SNP-SNP interactions. Highlights of IOBLPSO are the introduction of three strategies, namely, opposition-based learning, dynamic inertia weight, and a postprocedure. Opposition-based learning not only enhances the global explorative ability, but also avoids premature convergence. Dynamic inertia weight allows particles to cover a wider search space when the considered SNP is likely to be a random one and converges on promising regions of the search space while capturing a highly suspected SNP. The postprocedure is used to carry out a deep search in highly suspected SNP sets. Experiments of IOBLPSO are performed on both simulation data sets and a real data set of age-related macular degeneration, results of which demonstrate that IOBLPSO is promising in detecting SNP-SNP interactions. IOBLPSO might be an alternative to existing methods for detecting SNP-SNP interactions.

PMID: 26236727 [PubMed - in process] PMCID: PMC4509494

Mol Cytogenet. 2015 Aug 1;8:58. eCollection 2015.

Cytogenetic and molecular characterization of a recombinant X chromosome in a family with a severe neurologic phenotype and macular degeneration.

Magini P, Poscente M, Ferrari S, Vargiolu M, Bacchelli E, Graziano C, Wischmeijer A, Turchetti D, Malaspina E, Marchiani V, Cordelli DM, Franzoni E, Romeo G, Seri M.

BACKGROUND: Duplications of MECP2 gene in males cause a syndrome characterized by distinctive clinical features, including severe to profound mental retardation, infantile hypotonia, mild dysmorphic features, poor speech development, autistic features, seizures, progressive spasticity and recurrent infections. Patients with complex chromosome rearrangements, leading to Xq28 duplication, share most of the clinical features of individuals with tandem duplications, in particular neurologic problems, suggesting a major pathogenetic role of MECP2 overexpression.

RESULTS: We performed cytogenetic and molecular cytogenetic studies in a previously described family with affected males showing congenital ataxia, late-onset progressive myoclonic encephalopathy and selective macular degeneration. Microsatellite, FISH and array-CGH analyses identified a recombinant X chromosome with a deletion of the PAR1 region, encompassing SHOX, replaced by a duplicated segment of the Xq28 terminal portion, including MECP2.

CONCLUSIONS: Our report describes the identification of the actual genetic cause underlying a severe syndrome that previous preliminary analyses erroneously associated to a terminal Xp22.33 region. In the present family as well as in previously reported patients with similar rearrangements, the observed neurologic phenotype is ascribable to MECP2 duplication, with an undefined contribution of the other involved genes. Maculopathy, presented by affected males reported here, could be a novel clinical feature associated to Xq28 disomy due to recombinant X chromosomes, but at present the underlying pathogenetic mechanism is unknown and this potential clinical correlation should be confirmed through the collection of additional patients.

PMID: 26236399 [PubMed] PMCID: PMC4522089

Diet, lifestyle & low vision

Br J Ophthalmol. 2015 Aug 6. [Epub ahead of print]

Low luminance deficit and night vision symptoms in intermediate age-related macular degeneration.

Wu Z, Guymer RH, Finger RP.

BACKGROUND/AIMS: To determine the relationship between self-reported visual difficulties under low luminance conditions (night vision symptoms) and visual function measures in intermediate age-related macular degeneration (AMD).

METHODS: One hundred participants with bilateral intermediate AMD were examined in a prospective cross-sectional study with visual function measures including best-corrected visual acuity (BCVA), low luminance visual acuity (LLVA) and microperimetry in both eyes. A 10-item Night Vision Questionnaire (NVQ-10) was then used to determine the degree of self-reported night vision symptoms experienced by each participant. For analyses, low luminance deficit (LLD) was derived as the difference between LLVA and BCVA, and microperimetric mean sensitivity (MS; all points) and central sensitivity (CS; points within the central 1°) were determined. Rasch analysis was used to estimate the person measure of night vision symptoms, and its relationship with visual function parameters was determined.

RESULTS: NVQ-10 person measures were significantly associated with LLD (β coefficient=0.067, 95% CI 0.005 to 0.130, $p=0.034$), but not BCVA, LLVA, microperimetric MS or CS ($p\geq 0.090$). Participants with the highest degree of self-reported night vision symptoms (fourth quartile of person measure) had significantly

worse LLD than those with the least difficulty (first quartile of person measure; $p=0.019$).

CONCLUSIONS: In individuals with bilateral intermediate AMD, LLD was associated with self-reported night vision symptoms, suggesting that this measure may better capture the visual difficulties experienced by these individuals under low luminance conditions than the conventional measure of photopic visual acuity.

PMID: 26250520 [PubMed - as supplied by publisher]

Rev Panam Salud Publica. 2015 Jun;37(6):371-8.

Functional low vision in adults from Latin America: findings from population-based surveys in 15 countries.

Limburg H, Espinoza R, Lansingh VC, Silva JC.

OBJECTIVE: To review data on functional low vision (FLV) (low vision-visual acuity (VA) $< 6/18$ ($<20/60$) to $>$ perception of light (PL+) in the better eye-that is untreatable and uncorrectable) in adults aged 50 years or older from published population-based surveys from 15 countries in Latin America and the Caribbean.

METHODS: Data from 15 cross-sectional, population-based surveys on blindness and visual impairment (10 national and five subnational) covering 55 643 people > 50 years old in 15 countries from 2003 to 2013 were reanalyzed to extract statistics on FLV. Eleven of the studies used the rapid assessment of avoidable blindness (RAAB) method and four used the rapid assessment of cataract surgical services (RACSS) method. For the 10 national surveys, age-and sex-specific prevalence of FLV was extrapolated against the corresponding population to estimate the total number of people > 50 years old with FLV.

RESULTS: Age- and sex-adjusted prevalence of FLV in people > 50 years old ranged from 0.9% (Guatemala, Mexico, and Uruguay) to 2.2% (Brazil and Cuba) and increased by age. The weighted average prevalence for the 10 national surveys was 1.6%: 1.4% in men and 1.8% in women. For all 10 national studies, a total of 509 164 people > 50 years old were estimated to have FLV. Based on the 910 individuals affected, the main causes of FLV were age-related macular degeneration (weighted average prevalence of 26%), glaucoma (23%), diabetic retinopathy (19%), other posterior segment disease (15%), non-trachomatous corneal opacities (7%), and complications after cataract surgery (4%).

CONCLUSIONS: FLV is expected to rise because of 1) the exponential increase of this condition by age, 2) increased life expectancy, and 3) the increase in people > 50 years old. These data can be helpful in planning and developing low vision services for the region; large countries such as Brazil and Mexico would need more studies. Prevention is a major strategy to reduce FLV, as more than 50% of it is preventable.

PMID: 26245171 [PubMed - in process]

Philos Trans R Soc Lond B Biol Sci. 2015 Sep 19;370(1677).

Pulse trains to percepts: the challenge of creating a perceptually intelligible world with sight recovery technologies.

Fine I, Boynton GM.

Abstract: An extraordinary variety of sight recovery therapies are either about to begin clinical trials, have begun clinical trials, or are currently being implanted in patients. However, as yet we have little insight into the perceptual experience likely to be produced by these implants. This review focuses on methodologies, such as optogenetics, small molecule photoswitches and electrical prostheses, which use artificial stimulation of the retina to elicit percepts. For each of these technologies, the interplay between the stimulating technology and the underlying neurophysiology is likely to result in distortions of the perceptual experience. Here, we describe some of these potential distortions and discuss how they might be

minimized either through changes in the encoding model or through cortical plasticity.

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Autophagy. 2015 Aug 3:0. [Epub ahead of print]

The marine n-3 PUFA DHA evokes cytoprotection against oxidative stress and protein misfolding by inducing autophagy and NFE2L2 in human retinal pigment epithelial cells.

Johansson I, Monsen VT, Pettersen K, Mildenerger J, Misund K, Kaarniranta K, Schønberg S, Bjørkøy G.

Abstract: Accumulation and aggregation of misfolded proteins is a hallmark of several diseases collectively known as proteinopathies. Autophagy has a cytoprotective role in diseases associated with protein aggregates. Age-related macular degeneration (AMD) is the most common neurodegenerative eye disease that evokes blindness in elderly. AMD is characterized by degeneration of retinal pigment epithelial (RPE) cells and leads to loss of photoreceptor cells and central vision. The initial phase associates with accumulation of intracellular lipofuscin and extracellular deposits called drusen. Epidemiological studies have suggested an inverse correlation between dietary intake of marine n-3 polyunsaturated fatty acids (PUFAs) and the risk of developing neurodegenerative diseases, including AMD. However, the disease-preventive mechanism(s) mobilized by n-3 PUFAs is not completely understood. In human retinal pigment epithelial cells we find that physiologically relevant doses of the n-3 PUFA docosahexaenoic acid (DHA) induces a transient increase in cellular reactive oxygen species (ROS) levels that activates the oxidative stress response regulator NFE2L2/NRF2 (nuclear factor, erythroid derived 2, like 2). Simultaneously, there is a transient increase in intracellular protein aggregates containing SQSTM1/p62 (sequestosome 1) and an increase in autophagy. Pretreatment with DHA rescues the cells from cell cycle arrest induced by misfolded proteins or oxidative stress. Cells with a downregulated oxidative stress response, or autophagy, respond with reduced cell growth and survival after DHA supplementation. These results suggest that DHA both induces endogenous antioxidants and mobilizes selective autophagy of misfolded proteins. Both mechanisms could be relevant to reduce the risk of developing aggregate-associated diseases like AMD.

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