Macular Disease Foundation AUSTRALIA
Our focus is your vision

MD Research News

Issue 214

Tuesday 13 January, 2015

This free weekly bulletin lists the latest published research articles on macular degeneration (MD) and some other macular diseases as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases.

If you have not already subscribed, please email Rob Cummins at **research@mdfoundation.com.au** with 'Subscribe to MD Research News' in the subject line, and your name and address in the body of the email.

You may unsubscribe at any time by an email to the above address with your 'unsubscribe' request.

Drug treatment

Am J Ophthalmol. 2014 Dec 30. [Epub ahead of print]

Short-Term Changes in Choroidal Thickness After Aflibercept Therapy for Neovascular Age-related Macular Degeneration.

Koizumi H, Kano M, Yamamoto A, Saito M, Maruko I, Kawasaki R, Sekiryu T, Okada AA, Iida T.

PURPOSE: To investigate changes in choroidal thickness after aflibercept therapy for neovascular age-related macular degeneration (AMD).

DESIGN: Retrospective, consecutive, interventional case series.

METHODS: This study included 102 eyes of 102 patients with treatment-naïve neovascular AMD. All 102 eyes underwent 3 consecutive monthly 2.0 mg intravitreal aflibercept injections at baseline, 1 month, and 2 months. Choroidal thickness during 3 months were evaluated using either swept source optical coherence tomography (OCT) or enhanced depth imaging OCT.

RESULTS: Of the 102 eyes, 46 eyes (45.1%) were diagnosed as typical neovascular AMD and 56 eyes (54.9%) as polypoidal choroidal vasculopathy. After intravitreal aflibercept injections, the mean subfoveal choroidal thickness decreased from 252.0 ± 99.7 μm at baseline to 217.9 ± 95.6 μm at 3 months ($P < .0001$; percentage change from baseline, 86.5%). Mean choroidal thickness measured at 3 mm from the foveal center in the superior, inferior, temporal, and nasal directions also decreased significantly from 258.7 ± 85.9 μm to 236.4 ± 84.6 μm, 229.9 ± 93.0 μm to 208.6 ± 86.5 μm, 237.4 ± 86.5 μm to 214.6 ± 79.5 μm, and 183.7 ± 97.0 μm to 162.3 ± 90.6 μm, respectively ($P < .0001$ for all directions). All subtypes of neovascular AMD demonstrated a similar trend toward decreasing choroidal thickness during the follow-up period.

CONCLUSIONS: Choroidal thickness significantly decreased not only at the foveal center but also in the entire macula after 3 monthly intravitreal aflibercept injections for neovascular AMD.

PMID: 25555799 [PubMed]

Case Rep Ophthalmol. 2014 Nov 26;5(3):392-9.

Successful treatment of retinal angiomatous proliferation with intravitreal triamcinolone and ranibizumab injections in a 67-year-old male.

Haq A, Kapoor B, Logendran M, Reddy G.

Abstract: A 67-year-old male who presented to the eye casualty department with deterioration in his vision was diagnosed with retinal angiomatous proliferation. After initial deterioration with ranibizumab intravitreal

injections, we have demonstrated successful treatment and stabilised vision with ranibizumab and a single intravitreal triamcinolone injection. Stringent follow-up and top-up ranibizumab injections have stabilised his vision and have shown foveal improvement on optical coherence tomography imaging.

PMID: 25566060 [PubMed]

Mol Vis. 2014 Dec 19;20:1680-94.

Pharmacogenetic associations with long-term response to anti-vascular endothelial growth factor treatment in neovascular AMD patients.

Park UC, Shin JY, McCarthy LC, Kim SJ, Park JH, Chung H, Yu HG.

PURPOSE: To investigate the pharmacogenetic associations between the genetic risk variants of age-related macular degeneration (AMD) and long-term outcome after intravitreal anti-vascular endothelial growth factor (VEGF) treatment in Korean neovascular AMD patients.

METHODS: This prospective study included 394 treatment-naïve patients (394 eyes) that underwent intravitreal anti-VEGF treatment for neovascular AMD for at least 12 months. Patients were genotyped for 17 single nucleotide polymorphisms within 13 AMD-relevant genes. Initially, patients underwent three monthly injections of intravitreal ranibizumab and were retreated as needed with ranibizumab or bevacizumab. For each candidate polymorphism, genotypic associations with treatment outcome measures at months 12 and 24, including mean change in best-corrected visual acuity (BCVA) from baseline, visual gain of ≥15 letters, mean change in central subfield macular thickness (CSMT) from baseline on spectral domain optical coherence tomography (OCT), presence of fluid on OCT, and mean number of injections, were investigated using logistic or linear regression models with adjustment for non-genetic covariates.

RESULTS: At month 24, BCVA improved by 4.5 ± 22.5 letters and CSMT decreased by 69.4 ± 112.6 μm from baseline. Regression analysis with Bonferroni correction showed that the TT genotype for VEGFA rs3025039 was associated with a significantly higher chance of a visual gain of ≥15 letters at month 24 than other genotypes (odds ratio, 4.57; 95% confidence interval, 1.89 - 11.1; corrected p = 0.0434). As for tomographic outcome, the minor allele homozygotes for ARMS2 rs10490924 and HTRA1 rs1100638 (GG genotype for both) were associated with a larger CSMT reduction at month 12 than other genotypes, with borderline significance after Bonferroni correction (118.6 ± 132.7 μm versus 62.7 ± 89.7 μm, corrected p = 0.0656 for rs10490924; 115.7 ± 131.7 μm versus 63.6 ± 89.8 μm, corrected p = 0.0528 for rs11200638). No polymorphism showed a significant association with the number of injections.

CONCLUSIONS: In this Korean neovascular AMD cohort, treatment outcome after anti-VEGF was found to differ by the genotypes of VEGFA rs3025039, ARMS2 rs10490924, and HTRA1 rs11200638. Given more evidence of pharmacogenetic associations with the anti-VEGF agent, individualized therapeutic approaches based on genetic background could lead to optimal treatment in neovascular AMD.

PMID: 25558172 [PubMed - in process]

Sci Rep. 2015 Jan 7;5:7661.

The occurrence and progression of outer retinal tubulation in Chinese patients after intravitreal injections of ranibizumab.

Hua R, Liu L, Hu Y, Chen L.

Abstract: To investigate the occurrence and progression of outer retinal tubulation (ORT) in Chinese patients after intravitreal ranibizumab injections, using spectral domain optical coherence tomography (SD-OCT) with eye tracking function. 15 age related macular degeneration (AMD) and 6 polypoidal choroidal vasculopathy (PCV) eyes of 21 patients were enrolled and assessed by SD-OCT. One patient received photodynamic therapy (PDT) previously, and all patients received intravitreal injections of ranibizumab. At baseline, only one AMD eye (4.8%) showed ORT, which appeared as round or ovoid hyporeflective spaces

with hyperreflective borders. During the follow ups, ORT was identified in nine of 15 AMD eyes (60.0%) and one of six PCV eyes (16.7%). These new ORTs in 10 eyes were originated from the intraretinal fluid. Inner nuclear layer (INL), outer plexiform layer (OPL) and outer nuclear layer (ONL) were pulled down to form "cynapsis", separating each ORT. However, ORT in 3 eyes disappeared after intravitreal ranibizumab injections. This is the first observation on the occurrence and progression of ORT in Chinese AMD and PCV patients, in a point to point manner. The ORT could become stable or disappear after ranibizumab injections, and outer retina involved in the process of ORT formation.

PMID: 25564457 [PubMed - in process]

Med Arch. 2014 Jun;68(3):204-208.

Therapeutic Modalities of Exudative Age-related Macular Degeneration.

Mavija M, Alimanovic E, Jaksic V, Kasumovic SS, Cekic S, Stamenkovic M.

INTRODUCTION: Age-related macular degeneration (AMD) is a leading cause of irreversible serious vision damage in persons over 50 years of age. In treating AMD many medicaments are applied such as inhibitors of vascular endothelial growth factor (VEGF), have been very carefully included over the last few years after a series of study research.

AIMS: To analyze the past methods of treatment, discuss emerging therapies which could advance the treatment of exudative AMD. The past anti-VEGF therapies require frequent repetitions of administration, with uncertain visual acuity recovery, as not all patients react to anti-VEGF therapy. Consequently, there is a need to find out additional therapies which could improve the treatment of exudative AMD. The real aim in the treating of AMD is to prevent CNV development.

METHODS: A survey of the current clinical research and results in the field of the present and future treatments of exudative AMD.

RESULTS: There are many areas of research into new methods of the exudative AMD treatment.

CONCLUSION: The future therapies for exudative AMD treatment have a potential not only to reduce the frequency of administration and follow-up visits, but also to improve effects of treatment by targeting additional ways of CNV development, increasing the aptitude of target binding and extending durability of treatment.

PMID: 25568535 [PubMed - as supplied by publisher]

Annu Rev Pharmacol Toxicol. 2015 Jan 6;55:489-511.

Designed Ankyrin Repeat Proteins (DARPins): Binding Proteins for Research, Diagnostics, and Therapy.

Plückthun A.

Abstract: Designed ankyrin repeat proteins (DARPins) can recognize targets with specificities and affinities that equal or surpass those of antibodies, but because of their robustness and extreme stability, they allow a multitude of more advanced formats and applications. This review highlights recent advances in DARPin design, illustrates their properties, and gives some examples of their use. In research, they have been established as intracellular, real-time sensors of protein conformations and as crystallization chaperones. For future therapies, DARPins have been developed by advanced, structure-based protein engineering to selectively induce apoptosis in tumors by uncoupling surface receptors from their signaling cascades. They have also been used successfully for retargeting viruses. In ongoing clinical trials, DARPins have shown good safety and efficacy in macular degeneration diseases. These developments all ultimately exploit the high stability, solubility, and aggregation resistance of these molecules, permitting a wide range of conjugates and fusions to be produced and purified.

PMID: 25562645 [PubMed - in process]

Ophthalmic Surg Lasers Imaging Retina. 2015 Jan 1;46(1):91-4.

Intravitreal injection of ziv-aflibercept in patient with refractory age-related macular degeneration.

de Oliveira Dias JR, Xavier CO, Maia A, de Moraes NS, Meyer C, Farah ME, Rodrigues EB.

Abstract: The results of a patient with exudative age-related macular degeneration who received an intravitreal injection of ziv-aflibercept (Zaltrap; Sanofi-Aventis, Paris, France) in the right eye are described. A complete ocular examination as well as color fundus photography, optical coherence tomography, fluorescein angiography, microperimetry, full-field electroretinography, and multifocal electroretinography were performed and repeated 1 month later. The patient experienced subjective and objective improvement of visual acuity with a decrease in intraretinal and subretinal fluid. Microperimetric improvement also occurred. Electroretinographic changes were noted from baseline to the 30-day follow-up. No adverse events were observed at any time point. Ziv-aflibercept demonstrated short-term safety and efficacy after intravitreal administration for neovascular macular degeneration.

PMID: 25559518 [PubMed - in process]

Ophthalmic Surg Lasers Imaging Retina. 2015 Jan 1;46(1):87-90.

Retinal pigment epithelial tear after intravitreal aflibercept for neovascular age-related macular degeneration.

Sato T, Ooto S, Suzuki M, Spaide RF.

Abstract: Two eyes with neovascular age-related macular degeneration and a suboptimal response to intravitreal ranibizumab and bevacizumab developed tears after being switched to intravitreal aflibercept, a drug with enhanced binding characteristics to vascular endothelial growth factor. Both eyes had sub-retinal pigment epithelium (RPE) choroidal neovascularization adherent to the back surface of the RPE in the fibrovascular RPE detachment that showed increased contracture of the fibrovascular tissue following the use of aflibercept. The driving force to develop the tears may be related to the recently described angiofibrotic switch, which is governed by the ration of connective tissue growth factor to vascular endothelial growth factor.

PMID: 25559517 [PubMed - in process]

Ophthalmic Surg Lasers Imaging Retina. 2015 Jan 1;46(1):62-6.

Cost comparison of intravitreal aflibercept with bevacizumab and ranibizumab for the treatment of wet age-related macular degeneration.

Shaikh AH, Toussaint BW, Miller DM, Petersen MR, Foster RE, Riemann CD, Hutchins RK, Sisk RA.

BACKGROUND AND OBJECTIVE: To test the hypothesis that although intravitreal aflibercept (IVA) is expected to be more expensive, the extra cost of treatment would not result in additional vision gain compared with intravitreal bevacizumab (IVB) for the treatment of wet age-related macular degeneration.

PATIENTS AND METHODS: A retrospective chart review of patients receiving IVB or intravitreal ranibizumab (IVR) who were subsequently changed to IVA for active wet AMD.

RESULTS: Thirty-three eyes were included in the study. The mean number of IVB, IVR, and IVA injections per eye over a 6-month period was seven, six, and five, respectively. Visual outcomes were similar in all three groups at the end of the study period. The average drug cost of IVB, IVR, and IVA injections per eye over 6 months was $326, $11,400, and $9,720, respectively.

CONCLUSION: Aflibercept may allow a modest extension of the treatment interval, but cost makes IVA an expensive alternative without a visual benefit compared with IVB in patients with active wet AMD.

PMID: 25559511 [PubMed - in process]

Other treatment & diagnosis

Am J Ophthalmol. 2014 Dec 30. [Epub ahead of print]

Submacular Hemorrhage in Polypoidal Choroidal Vasculopathy Treated by Vitrectomy and Subretinal tissue Plasminogen Activator.

Kimura S, Morizane Y, Hosokawa M, Shiode Y, Kawata T, Doi S, Matoba R, Hosogi M, Fujiwara A, Inoue Y, Shiraga F.

PURPOSE: To evaluate vitrectomy with subretinal tissue plasminogen activator (t-PA) injection, and air tamponade, followed by intravitreal anti-vascular endothelial growth factor (VEGF) therapy for submacular hemorrhage in polypoidal choroidal vasculopathy (PCV).

DESIGN: Prospective, interventional case series.

METHODS: Setting: Two clinics. Patients: Fifteen eyes of 15 consecutive patients (mean age 72 ± 7 years) with submacular hemorrhage due to PCV. Inclusion criteria: PCV diagnosis with unorganized submacular hemorrhage greater than 500 μm thick. Exclusion criteria: submacular hemorrhage due to macular diseases (e.g. high myopia, typical age-related macular degeneration, retinal angiomatous proliferation, and angioid streaks). Intervention: Vitrectomy with 4,000 IU t-PA injected subretinally and fluid/air exchange. Patients remained facedown for 3 days after surgery. Anti-VEGF drugs were administered as exudative changes required. Main outcome measures: submacular hemorrhage displacement from the macula and changes in best-corrected visual acuities (BCVAs).

RESULTS: Mean time from onset to surgery was 9.5 ± 4.5 (range, 5-21) days. Mean follow-up period was 9.4 ± 3.1 (range, 6-17) months. Surgery successfully displaced submacular hemorrhages from the macula in all eyes. Mean BCVA at base line (0.98 ± 0.44) had improved significantly both 1 month after surgery (0.41 ± 0.25, $P<0.01$) and at final visits (0.23 ± 0.25, $P<0.001$). In all eyes, exudative retinal changes relapsed after surgery, but were completely resolved by anti-VEGF injections. No complications occurred in any patients.

CONCLUSION: Treating submacular hemorrhage with vitrectomy and subretinal t-PA injection, followed by intravitreal anti-VEGF therapy, is a promising strategy for improving visual acuity in PCV patients warranting further investigation.

PMID: 25555798 [PubMed - as supplied by publisher]

Duodecim. 2014;130(19):1991-9.

[Stem cell therapy of the eye]. [Article in Finnish]

Skottman H, Uusitalo EH.

Abstract: The structure of the eye and the currently available methods of ophthalmic surgery enable the development work on stem cell transplantations and their clinical implementation. For example the frequency of occurrence of age-related macular degeneration will increase significantly with the ageing population. Stem cell transplantations are therefore expected to be of considerable significance in the future treatment of ocular diseases. Clearly the farthest advance has been achieved with treatments developed for diseases of the cornea and the retina. Cell transplantations based on local stem cell transplantations are already in clinical use in some corneal diseases, and transplantations of retinal pigment epithelial cells differentiated from stem cells are being used in clinical studies.

PMID: 25558620 [PubMed - in process]

Conf Proc IEEE Eng Med Biol Soc. 2014 Aug;2014:162-5.

Automatic retinal interest evaluation system (ARIES).

Fengshou Yin, Wong DW, Ai Ping Yow, Beng Hai Lee, Ying Quan, Zhuo Zhang, Gopalakrishnan K, Ruoying Li, Jiang Liu.

Abstract: In recent years, there has been increasing interest in the use of automatic computer-based systems for the detection of eye diseases such as glaucoma, age-related macular degeneration and diabetic retinopathy. However, in practice, retinal image quality is a big concern as automatic systems without consideration of degraded image quality will likely generate unreliable results. In this paper, an automatic retinal image quality assessment system (ARIES) is introduced to assess both image quality of the whole image and focal regions of interest. ARIES achieves 99.54% accuracy in distinguishing fundus images from other types of images through a retinal image identification step in a dataset of 35342 images. The system employs high level image quality measures (HIQM) to perform image quality assessment, and achieves areas under curve (AUCs) of 0.958 and 0.987 for whole image and optic disk region respectively in a testing dataset of 370 images. ARIES acts as a form of automatic quality control which ensures good quality images are used for processing, and can also be used to alert operators of poor quality images at the time of acquisition.

PMID: 25569922 [PubMed - in process]

J Clin Med. 2014 Nov 28;3(4):1335-1356.

Endophenotypes for Age-Related Macular Degeneration: Extending Our Reach into the Preclinical Stages of Disease.

Gorin MB, Weeks DE, Baron RV, Conley YP, Ortube MC, Nusinowitz S.

Abstract: The key to reducing the individual and societal burden of age-related macular degeneration (AMD)-related vision loss, is to be able to initiate therapies that slow or halt the progression at a point that will yield the maximum benefit while minimizing personal risk and cost. There is a critical need to find clinical markers that, when combined with the specificity of genetic testing, will identify individuals at the earliest stages of AMD who would benefit from preventive therapies. These clinical markers are endophenotypes for AMD, present in those who are likely to develop AMD, as well as in those who have clinical evidence of AMD. Clinical characteristics associated with AMD may also be possible endophenotypes if they can be detected before or at the earliest stages of the condition, but we and others have shown that this may not always be valid. Several studies have suggested that dynamic changes in rhodopsin regeneration (dark adaptation kinetics and/or critical flicker fusion frequencies) may be more subtle indicators of AMD-associated early retinal dysfunction. One can test for the relevance of these measures using genetic risk profiles based on known genetic risk variants. These functional measures may improve the sensitivity and specificity of predictive models for AMD and may also serve to delineate clinical subtypes of AMD that may differ with respect to prognosis and treatment.

PMID: 25568804 [PubMed]

Pathogenesis

BMC Genomics. 2014 Dec 19;15 Suppl 12:S3.

Application of quantitative trait locus mapping and transcriptomics to studies of the senescence-accelerated phenotype in rats.

Korbolina EE, Ershov NI, Bryzgalov LO, Kolosova NG.

BACKGROUND: Etiology of complex disorders, such as cataract and neurodegenerative diseases including age-related macular degeneration (AMD), remains poorly understood due to the paucity of animal models, fully replicating the human disease. Previously, two quantitative trait loci (QTLs) associated with early cataract, AMD-like retinopathy, and some behavioral aberrations in senescence-accelerated OXYS rats were uncovered on chromosome 1 in a cross between OXYS and WAG rats. To confirm the findings,

we generated interval-specific congenic strains, WAG/OXYS-1.1 and WAG/OXYS-1.2, carrying OXYS-derived loci of chromosome 1 in the WAG strain. Both congenic strains displayed early cataract and retinopathy but differed clinically from OXYS rats. Here we applied a high-throughput RNA sequencing (RNA-Seq) strategy to facilitate nomination of the candidate genes and functional pathways that may be responsible for these differences and can contribute to the development of the senescence-accelerated phenotype of OXYS rats.

RESULTS: First, the size and map position of QTL-derived congenic segments were determined by comparative analysis of coding single-nucleotide polymorphisms (SNPs), which were identified for OXYS, WAG, and congenic retinal RNAs after sequencing. The transferred locus was not what we expected in WAG/OXYS-1.1 rats. In rat retina, 15442 genes were expressed. Coherent sets of differentially expressed genes were identified when we compared RNA-Seq retinal profiles of 20-day-old WAG/OXYS-1.1, WAG/OXYS-1.2, and OXYS rats. The genes most different in the average expression level between the congenic strains included those generally associated with the Wnt, integrin, and TGF-β signaling pathways, widely involved in neurodegenerative processes. Several candidate genes (including Arhgap33, Cebpg, Gtf3c1, Snurf, Tnfaip3, Yme1l1, Cbs, Car9 and Fn1) were found to be either polymorphic in the congenic loci or differentially expressed between the strains. These genes may contribute to the development of cataract and retinopathy.

CONCLUSIONS: This study is the first RNA-Seq analysis of the rat retinal transcriptome generated with 40 mln sequencing read depth. The integration of QTL and transcriptomic analyses in our study forms the basis of future research into the relationship between the candidate genes within the congenic regions and specific changes in the retinal transcriptome as possible causal mechanisms that underlie age-associated disorders.

PMID: 25563673 [PubMed - in process]

J Chin Med Assoc. 2014 Dec 31. [Epub ahead of print]

Using induced pluripotent stem cell-derived conditional medium to attenuate the light-induced photodamaged retina of rats.

Chang H, Hung K, Hsu C, Lin T, Chen S.

BACKGROUND: Light injury to photoreceptor cells and retinal pigment epithelium may lead to oxidative stress and irreversible degeneration of retina, especially degeneration of the high energy-demanded macula. The model of retinal photodamage could be applied to age-related macular degeneration and other degenerative retinal diseases for exploring new treatments. Based on broadly investigated induced pluripotent stem cells (iPSC) in the field of retinal degeneration, we aimed to clarify further how the interaction progresses between iPSC-conditional medium (CM) and light-damaged retina.

METHODS: iPSCs were generated from murine embryonic fibroblasts of C57/B6 mice by retroviral transfection of three factors: Oct4, Sox2, and Klf4. Cytokine array was performed to analyze the components of CM. Sprague-Dawley rats receiving white light exposure to retina were viewed as an animal model of light injury. The rats were divided into four subgroups: light-injured rats receiving intravitreal injection of iPSC-CM, apoptotic iPSC-CM, or sodium phosphate buffer (PBS); and a control group without light damage. The electroretinography and thickness of outer nuclear layer were measured to document the therapeutic effects in each condition. Apoptosis arrays for detecting annexin V and caspase 3 were performed in the retinal tissues from each group.

RESULTS: Murine embryonic fibroblasts were induced into iPSCs and expressed the marker genes similar to embryonic stem cells. These iPSCs can differentiate into Embryoid bodies (EBs), three germ layers in vitro and develop teratoma in severe combined immunodeficiency mice. The quantitative polymerase chain reaction of our iPSC-CM showed significantly elevated fibroblast growth factor-2, glial cell-derived neurotrophic factor, and insulin-like growth factor-binding proteins-1, -2, and -3. Compared to rats without photodamage, the light-injured rats receiving iPSC-CM had less reduction of outer nuclear layer thickness on Day 21 than other groups treated with either PBS or apoptotic iPSC-CM. In the same animal model, both a- and b-waves of electroretinography measurement in the group treated with iPSC-CM were

significantly maintained compared to the control group and others with apoptotic iPSC-CM or PBS treatment. The apoptosis assay also demonstrated lower levels of annexin V and caspase 3 in the group with iPSC-CM treatment than in other groups presenting increasing apoptotic markers.

CONCLUSION: The conditional medium of iPSCs contains plenty of cytoprotective, immune-modulative and rescue chemicals, contributing to the maintenance of neuronal function and retinal layers in light-damaged retina compared with apoptotic iPSC-CM and PBS. The antiapoptotic effect of iPSC-CM also shows promise in restoring damaged neurons. This result demonstrates that iPSC-CM may serve as an alternative to cell therapy alone to treat retinal light damage and maintain functional and structural integrity of the retina.

PMID: 25557467 [PubMed - as supplied by publisher]

J Biol Chem. 2015 Jan 2. [Epub ahead of print]

Efficient delivery and functional expression of transfected modified mRNA in human Embryonic Stem Cell-derived Retinal Pigmented Epithelial cells.

Hansson ML, Albert S, Gonzalez Somermeyer L, Peco R, Mejia-Ramirez E, Montserrat N, Izpisua Belmonte JC.

Abstract: Gene- and cell-based therapies are promising strategies for the treatment of degenerative retinal diseases such as age-related macular degeneration (AMD), Stargardt disease and Retinitis Pigmentosa. Cellular engineering before transplantation may allow the delivery of cellular factors that can promote functional improvements such as increased engraftment or survival of transplanted cells. A current challenge in traditional DNA-based vector transfection is to find a delivery system that is both safe and efficient, but using mRNA as an alternative to DNA can circumvent these major roadblocks. In this study, we show that both unmodified and modified mRNA can be delivered to Retinal Pigmented Epithelial (RPE) cells with a high efficiency, when compared with conventional plasmid delivery systems. On the other hand, administration of unmodified mRNA induced a strong innate immune response, which was almost absent when using modified mRNA. Importantly, transfection of mRNA encoding a key regulator of RPE gene expression, Microphthalmia-associated transcription factor (MITF), confirmed the functionality of the delivered mRNA. Immunostaining showed that transfection with either type of mRNA led to the expression of roughly equal levels of MITF, primarily localized in the nucleus. Despite these findings, qRT-PCR analyses showed that the activation of the expression of MITF's target genes was higher following transfection with modified mRNA when compared with unmodified mRNA. Our findings therefore show that modified mRNA transfection can be applied to human embryonic stem cell-derived RPE cells, and that the method is safe, efficient and functional.

PMID: 25555917 [PubMed - as supplied by publisher]

Conf Proc IEEE Eng Med Biol Soc. 2014 Aug;2014:414-7.

Time-varying pulse trains limit retinal desensitization caused by continuous electrical stimulation.

Davuluri NS, Weiland JD.

Abstract: An epiretinal prosthesis aims to restore functional vision in patients suffering from retinal degeneration caused by diseases such as Retinitis Pigmentosa (RP) and Age-Related Macular Degeneration (AMD). These diseases result in the loss of photoreceptors but bipolar, amacrine and ganglion cells survive at high rates and can be electrically activate to produce the sensation of light. Continuous application of biphasic stimulus pulses results in desensitization of the retina. In humans, this manifests as decreased brightness and increased stimulus thresholds. This study presents an in vivo model of retinal desensitization caused by continuous electrical stimulation and describes a novel stimulation pattern that limit desensitization.

PMID: 25569984 [PubMed - in process]

Antioxid Redox Signal. 2015 Jan 4. [Epub ahead of print]

Isolevuglandin Adducts In Disease.

Salomon R, Bi W.

Significance: A diverse family of lipid-derived levulinaldehydes, isolevuglandins (isoLGs), is produced by rearrangement of endoperoxide intermediates generated through both cyclooxygenase (COX) and free radical-induced cyclooxygenation of polyunsaturated fatty acids and their phospholipid esters. The formation and reactions of isoLGs with other biomolecules has been linked to alcoholic liver disease, Alzheimer's disease, age-related macular degeneration, atherosclerosis, cardiac arythmias, cancer, end-stage renal disease, glaucoma, inflammation of allergies and infection, mitochondrial dysfunction, multiple sclerosis, and thrombosis. This review chronicles progress in understanding the chemistry of isoLGs, detecting their production in vivo and understanding its biological consequences.

Critical Issues: IsoLGs have never been isolated from biological sources because they form adducts with primary amino groups of other biomolecules within seconds. Chemical syn¬thesis enabled investigation of isoLG chemistry and detection of isoLG adducts present in vivo.

Recent Advances: The first peptide mapping and sequencing of an isoLG-modified protein present in human retina identified the modification of a specific lysyl residue of the sterol C27-hydroxylase Cyp27A1. This residue is preferentially modified by iso[4]LGE2 in vitro causing loss of function. Adduction of less than one equivalent of isoLG can induce COX-associated oligomerization of the amyloid peptide Aβ1-42. Adduction of isoLGE2 to phosphatidylethanolamines causes gain of function converting them into proinflammatory isoLGE2-PE agonists that foster monocyte adhesion to endothelial cells.

Future Directions: Among the remaining questions on the biochemistry of isoLGs are the dependence of biological activity on isoLG isomer structure, the structures and mechanism of isoLG derived protein-protein and DNA-protein cross-link formation and its biological consequences.

PMID: 25557218 [PubMed - as supplied by publisher]