Retina (DJ Version) |WORK|

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The eye is continuously under oxidative stress due to high metabolic activity and reactive oxygen species generated by daily light exposure. The redox-sensitive protein DJ-1 has proven to be essential in order to protect retina and retinal pigment epithelium (RPE) from oxidative-stress-induced degeneration. Here, we analyzed the specific role of Müller cell DJ-1 in the adult zebrafish retina by re-establishing Müller-cell-specific DJ-1 expression in a DJ-1 knockout retina. Loss of DJ-1 resulted in an age-dependent retinal degeneration, including loss of cells in the ganglion cell layer, retinal thinning, photoreceptor disorganization and RPE cell dysfunction. The degenerative phenotype induced by the absence of DJ-1 was inhibited by solely expressing DJ-1 in Müller cells. The protective effect was dependent upon the cysteine-106 residue of DJ-1, which has been shown to be an oxidative sensor of DJ-1. In a label-free proteomics analysis of isolated retinas, we identified proteins differentially expressed after DJ-1 knockout, but with restored levels after Müller cell DJ-1 re-insertion. Our data show that Müller cell DJ-1 has a major role in protecting the retina from age-dependent oxidative stress. We have previously reported the expression of Parkinson disease-associated genes encoding α-synuclein, parkin and UCH-L1 in the retina across mammals. DJ-1, or parkinsonism-associated deglycase, is a redox-sensitive protein with putative roles in cellular protection against oxidative stress, among a variety of functions, acting through distinct pathways and mechanisms in a wide variety of tissues. Its function in counteracting oxidative stress in the retina, as it occurs in Parkinson and other human neurodegenerative diseases, is, however, poorly understood. In the present

study, we address the expression of DJ-1 in the mammalian retina and its putative neuroprotective role in this tissue in a well-known model of parkinsonism, the rotenone-treated rat. As a result, we demonstrate that the DJ1 gene is expressed at both mRNA and protein levels in the neural retina and retinal pigment epithelium (RPE) of all mammalian species studied. We also present evidence that DJ-1 functions in the retina as a sensor of cellular redox homeostasis, which reacts to oxidative stress by increasing its intracellular levels and additionally becoming oxidized. Levels of α-synuclein also became upregulated, although parkin and UCH-L1 expression remained unchanged. It is inferred that DJ-1 likely exerts in the retina a potential neuroprotective role against oxidative stress, including α-synuclein oxidation and aggregation, which should be operative under both physiological and pathological conditions. Currently, the most common virus vector used in gene therapy research for ophthalmologic diseases is the adeno-associated virus (AAV) vector, which has been used in a number of successful preclinical and clinical studies (Bainbridge et al., 2008; Hauswirth et al., 2008; Maguire et al., 2008; Jacobson et al., 2012; MacLaren et al., 2014; Hoxha et al., 2016). Since AAV vectors can transduce genes into non-dividing cells such as neurons, it is advantageous for tissues such as the retina. As a virus, AAV is an excellent vector since it has low cytotoxicity and pathogenicity. In December 2017, the FDA approved the first gene therapy product using AAV for an inherited retinal disease (Russell et al., 2017; Miraldi Utz et al., 2018). Vector systems based on other AAV serotypes with more efficient gene transduction and different cell and tissue specificities are being investigated. In addition to the

naturally occurring series of AAVs, novel recombinant AAV capsid variants with efficient gene transfer and tropism have been generated recently either by rational design or directed evolution (Carvalho & Vandenberghe, 2015). It is important to continuously evaluate novel AAV vectors for human gene therapy and its basic research, because cell-type-specific gene introduction tailored to each disease will make treatment more efficient and minimize the immunologic sequelae, and increased packaging capacity expands therapeutic gene options (Taymans et al., 2007; Zaiss & Muruve, 2008). Although AAV-2 is currently most frequently used, the serotype cannot introduce genes into photoreceptors with intravitreal injection (Dalkara et al., 2009; Yin et al., 2011). Intravitreal injection is less invasive and a route of administration performed routinely for clinical human subjects. New AAV capsids that penetrate photoreceptors with intravitreal injection can be a revolution in the retinal gene therapy. (A, B) Representative fundus photographs show EGFP expression in live mice from 1 through 12 weeks after the AAV injection. A: AAV-2-CAGGS-EGFP, B: AAV-DJ-CAGGS-EGFP. (C, D) Quantification of EGFP fluorescence intensity from fundus fluorescent photographs. The mean fluorescence values were measured over the circular imaging range. (E, F) Representative confocal image across the RGC layer of flat mounted mouse retina transduced with AAV-2-CAGGS-EGFP or AAV-DJ-CAGGS-EGFP at 4 weeks after injection, co-labeled with Brn3a (red). (G) Quantification of the EGFP-positive rate in Brn3a-positive cells. The cells were counted in a region 212-μm-square on each top, bottom, left, and right side of the flat-mounted retina and averaged. Error bars represent the

standard error of the mean. Scale bars, 50 μm in E and F. *** p In case you missed it, Native Instruments announced had announced a complete rewrite of the Traktor software earlier this year at NAMM. Based on the design and feature set of Traktor DJ for iOS, Traktor DJ 2 is set to be the future of Traktor, starting with a beginner feature set and expanding further as more versions roll out in the future. Throughout his career, Dr. Chisholm has been involved in several areas of both basic science and clinical retinal research. He has authored and co-authored several articles in peer review journals including the Canadian Journal of Ophthalmology, the Canadian Medical Association Journal, Cornea, and the New England Journal of Medicine. **Purpose** : DJ-1 is an antioxidant protein highly expressed in RPE and inner segment of photoreceptors in retina of adult mice. Previous studies from our lab have established that lack of DJ-1 increases susceptibility of RPE and retina to oxidative stress in mice. Here, we analyzed pro-survival signaling in RPE and retina of young DJ-1 KO mice and control. **Results** : Injection of DJ-1 KO mice with low level oxidative stress (10mg/kg NaIO3) resulted in morphological retinal and RPE degeneration but not in control mice. In baseline conditions, 248 proteins were unique to control whereas only 57 proteins were unique to the DJ-1 KO RPE. Among the total detected proteins, 3 % of the proteins were significantly upregulated, 5 % of the proteins were significantly downregulated in DJ-1 KO RPE compared to control. In the retina, 158 proteins were unique to control whereas 196 proteins were unique to DJ-1 KO mice. Of the total detected proteins, 3% of the proteins were significantly upregulated, 2% were significantly downregulated in DJ-1 KO retina compared to

control. Pathway analyses detected cell death and survival as one of the top molecular and cellular functions changed in the DJ-1 KO retina and RPE. Validation of the proteomics data by Western blot analysis detected lower pro-survival molecule AKT signal in DJ-1 KO RPE compared to control. The most common virus vector used in gene therapy research for ophthalmologic diseases is the adeno-associated virus (AAV) vector, which has been used successfully in a number of preclinical and clinical studies. It is important to evaluate novel AAV vectors in animal models for application of clinical gene therapy. The AAV-DJ (type 2/type 8/type 9 chimera) was engineered from shuffling eight different wild-type native viruses. In this study, we investigated the efficiency of gene transfer by AAV-DJ injections into the retina. One microliter of AAV-2-CAGGS-EGFP or AAV-DJ-CAGGS-EGFP vector at a titer of 1.4 × 10e12 vg/ml was injected intravitreally or subretinally in each eye of C57BL/6 mice. We evaluated the transduction characteristics of AAV-2 and -DJ vectors using fluorescence microscopy and electroretinography. The results confirmed that AAV-DJ could deeply transfer gene to photoreceptor layer with intravitreal injection and has an efficient gene transfer to various cell types especially the Mueller cells in the retina. Retinal function was not affected by AAV-DJ infection or ectopic EGFP expression. The AAV-DJ vector efficiently induces the reporter gene in both the inner and outer murine retina without functional toxicity. These data indicated that the AAV-DJ vector is a useful tool for the gene therapy research targeting retinal disorders. The only way that I see that the new retina display MBP is better is if you do a LOT of photography or video editing. Even then, it would've been better for Apple to simply introduce a

dedicated retina-display monitor. Our laboratory focuses on the mechanisms of neurodegeneration in glaucoma, the leading cause of irreversible blindness worldwide. Glaucoma blinds through the gradual loss of retinal ganglion cell neurons and their axons, which comprise the optic nerve. The loss of these neurons affects a major portion of the brain, which receives signals from the retina. Insight into the early molecular cascades involved in the degenerative process hopefully will lend insight into the identification of novel therapeutic targets. The laboratory uses systems, cellular and molecular approaches to investigate how risk factors in glaucoma, such as age and elevated ocular pressure, contribute to neurodegeneration in the disease and to test new treatments. The axon of the retinal ganglion cell neuron projects to various nuclei of the brain through the optic nerve. In glaucoma, these these projections degenerate in response to key risk factors like aging and elevated ocular pressure.

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