Int J Clin Exp Pathol 2018;11(8):4221-4229
www.ijcep.com /ISSN:1936-2625/IJCEP0073997

Original Article

Down-regulation of Fra-2 alleviates light-induced retina damage by inhibiting the PARP-1/AIF pathway

Juling Lv, Yiqiao Xing

Department of Ophthalmology, Renmin Hospital of Wuhan University, Wuhan, Hubei Province, P. R. China

Received February 4, 2018; Accepted July 3, 2018; Epub August 1, 2018; Published August 15, 2018

Abstract: Visible light has been previously demonstrated to induce retina damage and retinal ganglion cell (RGC) death through the mitochondrial pathway. The *Fra-2* gene was detected as a transcriptional regulator, but whether it is involved in light-induced retina damage remains unclear. In this study, we investigated the effect of Fra-2 on a light-induced mouse retinal damage model and in vitro RGC-5 cells. Tissues lysed and ripped were observed in the inner nuclear layer (INL) and the ganglion cell layer (GCL) of the retina after mice were exposed to light for 12 h. Light exposure significantly increased the expression of Fra-2 and PARP-1 in a time-dependent manner. Light exposure or the up-regulation of Fra-2 significantly increased the apoptosis and decreased the proliferation of RGC-5 cells. At the same time, the down-regulation of Fra-2 or NU1025 exposure significantly inhibited light-induced RGC-5 cell apoptosis and induced the proliferation of light-induced RGC-5 cells. Light exposure or up-regulation of Fra-2 significantly increased the expression of PARP-1 and nuclear AP-1, but the down-regulation of Fra-2 or NU1025 exposure significantly attenuated those protein expressions. Those results suggest that Fra-2 is involved in light induced retinal damage and causes cell death by the activation of the PARP-1/AIF signaling pathway. Down-regulation of Fra-2 might alleviate light-induced retinal damage via inhibiting PARP-1-independent AIF release.

Keywords: Retinal damage, Fra-2, PARP-1, apoptosis, light exposure

Introduction

The light-induced retinal damage model is well established in retinal degeneration research. The pathologic and morphological changes of several common degenerative diseases, such as age-related macular degeneration and retinitis pigmentosa, are similar to light-induced retinal damage [1]. The light-induced retinal damage model is widely used in research about the factors leading to photoreceptor death, in the evaluation of retinal degenerative events, and in neuroprotective therapies for oxidative stress [2, 3]. Light impinging on the retina is toxic to retinal cells and induces degeneration of cell functions, eventually leading to ischemia, glaucoma, and diabetic retinopathy [4]. Retinal ganglion cells (RGCs), as the ultimate neurons in the retina, play an important role in light response, as visual signals collect from layers of nerve cells and amacrine cells and transfer light into electrochemical signals in the brain [5]. Excessive light has been reported to enhance the progression and severity of human age-related macular degeneration and perhaps to induce retinitis pigmentosa [6]. Experimental studies have suggested that light exposure exerts a negative effect on the survival of RGCs and photoreceptors [7, 8]. At the late stages of light exposure, in the innermost layer, the retinal vessels overlying the nerve fiber layers drag, compress, and sever the RGC axons, finally leading to the death of these neurons [9, 10]. Therefore, the death of RGCs in the light-induced retinal damage model is not secondary to photoreceptor degeneration, but rather to retinal remodeling [1].

Damaging light can be absorbed by the visual pigment rhodopsin, creating an intracellular death signal that results in the activation of AP-1 [11]. The *fos*-related antigen-2 (*far*-2) gene is a transcriptional regulator that encodes a member of the AP-1 family, which is comprised of proteins related to the products of two proto-oncogenes, *c-fos* and *c-jun* [12]. The genomic and/or cDNA clones of fra-2 have now been isolated for humans, chickens, and mice, and the gene structure is evolutionary well conserved, as is the encoded protein [13, 14]. In a variety

of animal tissues, the *fra*-2 gene showed high expression levels [14]. The fra-2 protein can form heterodimeric complexes with the members of Jun family, which can bind with high affinity to the AP-1 and effect transcriptional activation [15]. It was reported that overexpression of *fra*-2 results in weak transformation of chicken embryo fibroblasts but no transformation of rat fibroblast lines [16]. In many tumor cells, the fra-1, fra-2 and c-Fos proteins are capable of activating the transcription of a series of genes with a certain degree of specificity [17]. It suggested that fra-1 and fra-2 are involved in the maintenance and progression of the transformed state, and that this property is unconnected to their similar ability to transactivate a synthetic AP-1 dependent reporter in transient transfection assays [18].

Poly (ADP-ribose) polymerase 1 (PARP-1), as a conservation nuclear enzyme, plays an important role in DNA repairing. Under stress conditions, PARP-1 leads to a massive synthesis of NAD^+ which results in intracellular NAD^+ and ATP being depleted rapidly. Subsequently, the apoptosis inducing factor (AIF) translocates from the mitochondria to the cytosol and nucleus, and AIF binds with DNA and RNA to induce caspase-independent chromatinolysis in the nucleus [19, 20]. More recent evidence has shown that the apoptosis of RGC-5 cells induced by light exposure involved the activation of PARP-1 and AIF [21, 22]. NU1025, as a competitive PARP-1 inhibitor, can compete with NAD^+ and interferes with the activity binding site of the enzyme [23]. Therefore, PARP-1 inhibitors are widely used in disease research [24, 25].

In the present study, light-induced mouse retinal damage models were established, and fra-2 overexpression or interference vectors were transfected to RGC-5 cells. The expressions of AP-1 and PARP-2 were used to evaluate the cell damage. The aim of the present study was to demonstrate the effects of fra-2 on light induced retinal damage.

Materials and methods

Animals and light-induced retinal damage model

All procedures involving animals adhered to the Association for Research in Vision and Ophthalmology statement for the use of animals in ophthalmic and vision research. Male mice aged 6-8 weeks were obtained from the Hubei Provincial Center for Disease Control and Prevention (Hubei, China), and acclimatized in our laboratory for two weeks before the experimental manipulation. Mice were reared in cage, with dry pellets and intermittent feeding of green fodder in a 12:12 h light/dark cycle.

Before the light exposure, 15 mice were dark adapted for 24 h and randomly divided into 5 groups: the control group and 4 light exposure groups (6 h, 12 h, 24 h, 36 h), n=3. After pupil dilation with compound tropicamide, 12 mice were exposed to white light with 2600 lux for 6 h, 12 h, 24 h and 36 h, respectively. After exposure, all mice were sacrificed, and we gathered the eyes for Western blot and hematoxylin-eosin (HE) staining.

HE staining

Mice were fasted overnight (not less than 12 hours), and intraperitoneally anesthetized and euthanized with sodium pentobarbital at 40 mg/1000 g weight. The eyes of the mice were sampled and placed in 10 ml 10% formalin. After 24 h, the fixative was aspirated and replaced with 10 ml 10% formalin and stored at 4°C. The tissues were embedded in paraffin wax and sections were stained with hematoxylin-eosin.

Western blot

A Western blot analysis was performed to determine the expression of the fra-2, PARP-1 and AP-1 proteins in mouse eyes or RGC-5 cells. Tissue or cells were homogenized with a lysis buffer and centrifuged at 12000 g for 15 min. The protein concentration was determined by a BCA kit (Bioswamp, China). Equal amounts of protein (30 μg) were separated by 10% SDS-polyacrylamide gel and then transferred onto PVDF membranes (Millipore, Massachusetts, USA). The membranes were blocked for 2 h at room temperature with 5% skim milk in Tris-buffered saline (20 mmol/L Tris, 500 mmol/L NaCl and 0.05% Tween 20). Subsequently, the membranes were incubated with specific antibodies overnight at 4°C, including the mouse anti-fra-2 antibody (GM-EP6067, MBL, Japan, 1:1000 dilution), the mouse anti-PARP-1 antibody (PAB12768, Bio-Swamp, China, 1:1000 dilution), and the mouse anti-AP-1 antibody (GW21143, Sigma, USA, 1:2000 dilution). The

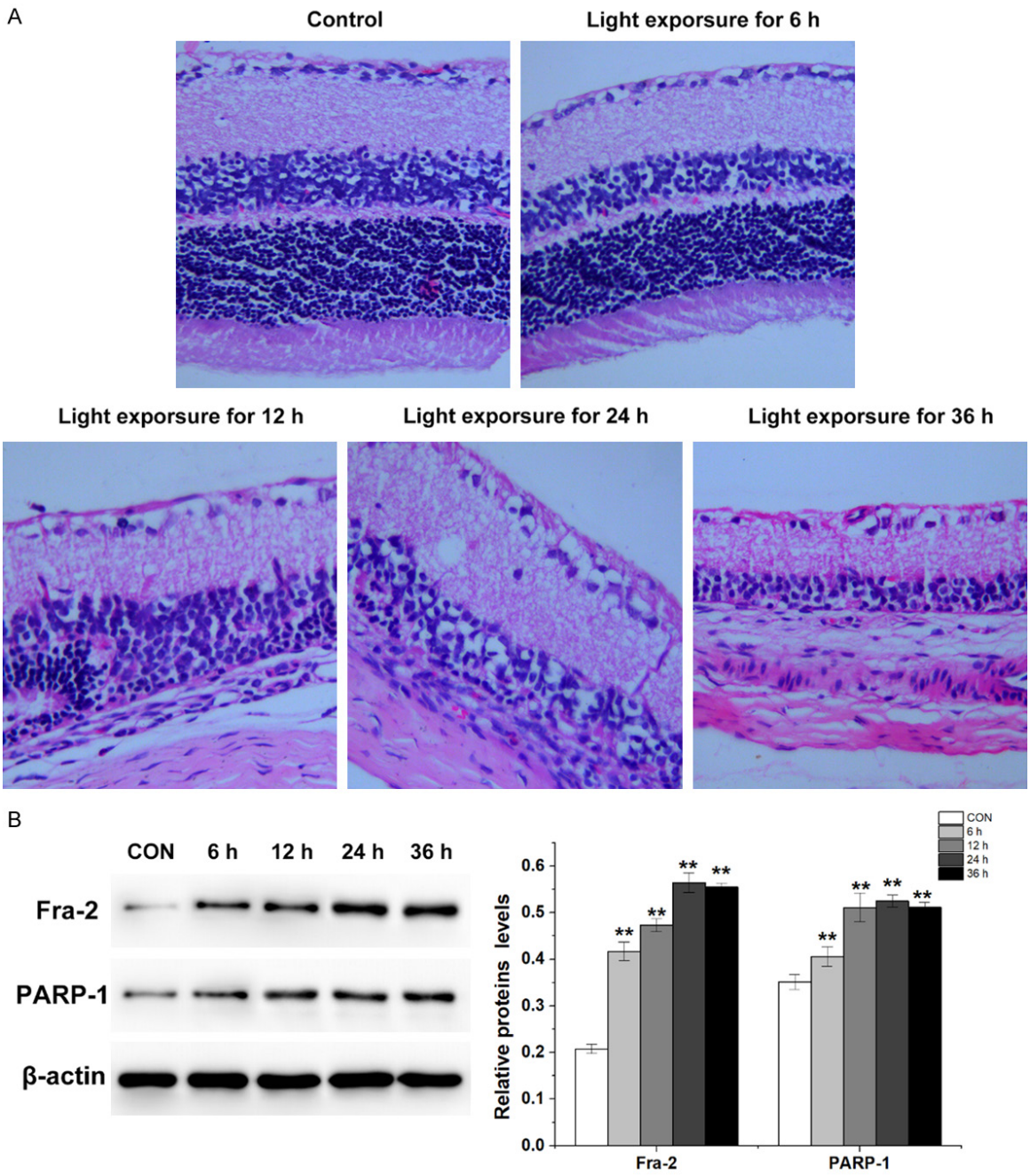

Figure 1. A. HE staining for the evaluation of light-induced retinal injury (400 × magnification). After light exposure for 12 h, mouse retina underwent severe destruction and major damage appeared in the inner nuclear (INL) and the ganglion cell (GCL) layers, showing tissue lysed and ripped. B. Light exposure induced the expression of fra-2 and PARP-1 in mice retinas. Bands were quantified using Quantity One 5.0 and the fold changes in each protein to β-actin ratio are shown. Data are shown by means ± SD (n=3); **P<0.01 versus CON group. CON: control group; 6 h: light exposure for 6 h group; 12 h: light exposure for 12 h group; 24 h: light exposure for 24 h group; 36 h: light exposure for 36 h group.

anti-β-actin antibody (GTX100118, GeneTex, USA, 1:10000 dilution) was selected as an internal reference. Then, the membranes were washed with Tris-buffered saline and incubated in secondary antibodies for 2 h at room temperature. Immunoreactivity was visualized by colorimetric reaction using an ECL substrate buffer (Millipore, Massachusetts, USA). Membranes were scanned with Gel Doz EZ imager (BIO-RAD, USA).

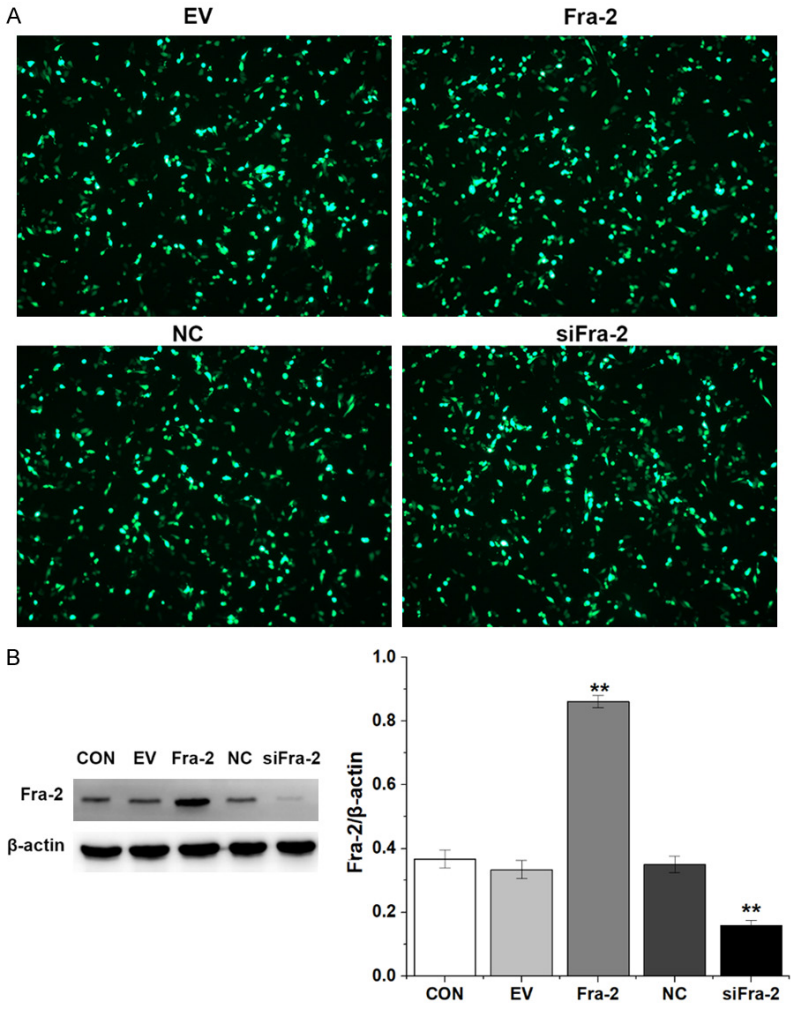

Figure 2. A. The overexpression or interference vector was inserted into RGC-5 cells and detected by fluorescence microscopy. B. The protein levels of Fra-2 in RGC-5 cells after being transfected with a vector. All values are expressed as the means ± SD (n=3). **P<0.01 versus CON group. CON: control group; EV: empty vector; fra-2: fra-2 overexpression group; NC: negative group; siFra-2: fra-2 down-regulation group.

Cell culture and vectors transfection

RGC-5 cells were purchased from American Type Culture Collection and were grown in a DMEM medium (Invitrogen, China) supplemented with 10% fetal bovine serum, 100 U/ml penicillin, and 100 μg/ml streptomycin in a humidified atmosphere of 95% air and 5% CO_2 at 37°C. The cells were divided into a control group (CON), a fra-2 up-regulation group (Fra-2), an empty vector group (EV), a fra-2 down-regulation group (siFra-2), and a negative control group (NC). The Fra-2 gene was amplified by primers (Fra-2F: 5'-CGTCAATGGGTGGAGTATTTACGG-3', Fra-2R: 5'-CGCCTGCAGCTTCTCTGTCAGCTC-3') and was inserted into the pGPU6/GFP/Neo vector site to construct the overexpression vector pGPU6/GFP/Neo-Fra-2; Negative control pGPU6/GFP/Neo-shNC (target sequence: GTTCTCCGAACGTGTCACGT), and fra-2 interference vectors pGPU6/GFP/Neo-siFra-2 (target sequence: CTGCGATTGGCTCTCACTCTGTTTCC), were purchased from GenePharma (China). Cells were transfected with the plasmid using Lipofectamine 2000 (Invitrogen) according to the manufacturer's instructions.

Cell proliferation was measured by MTT test; cell apoptosis was evaluated by the Annexin V-FITC/PI (propidium iodide) flow cytometry kit; the protein levels of Fra-2, PARA-1 and AP-1 were evaluated by Western blot; the locations of PARP-1 and AP-1 in the RGC-5 cells were evaluated by immunofluorescence.

Light exposure

RGC-5 cells were randomly divided into 4 groups: the control group (CON), the light exposure group (LE), the siFra-2 + LE (Fra-2 + NU1025) group, and the light exposure + PARP inhibitor group (200 μM NU1025) (LE + NU1025). The light exposure of RGC-5 cells was performed as previously described [26]. A normal culture incubator was equipped with two 8-Watt strip-lights that were completely covered with 2C UV filters that excluded light with a wavelength below 400 nm. The intensity of the light directed onto the cells was determined by using a digital lux meter (LX-101; Lutron Electronic, London, UK).

Cell proliferation was measured by an MTT test; cell apoptosis was evaluated by an AnnexinV-FITC/PI (propidium iodide) flow cytometry kit;

the protein levels of PARP-1 and AP-1 were evaluated by Western blot.

MTT assay

Cell proliferation was measured using an MTT assay. RGC-5 cells were seeded into 96-well plates and 20 μl MTT (5 mg/ml, sigma) was added to each culture and incubated for 4 to 6 h. At the end of the incubation period the medium was removed and 150 μl DMSO was added to each well. After shaking at low speed for 10 min, the absorbance of converted dye was measured at a wavelength of 490 nm.

Statistical analysis

The statistical differences of the experimental data were performed by Dunnett's one-way analysis of variance (ANOVA) using the SPSS 19.0 software package. Differences were considered as statistically significant at $P<0.05$ and very significant at $P<0.01$. All results were expressed as mean ± SD.

Results

Light exposure induced damage and fra-2 and PARP-1 protein expression in mice retinas

Histological analysis showed that mice retinas underwent severe destruction after intensive light exposure for 12 h. The major damage appeared in the inner nuclear layer (INL) and the ganglion cell layer (GCL), showing tissue lysed and ripped. In the control group and light exposure for 6 h group, all layers of the retina were attached tightly (**Figure 1A**).

Compared with the control group, the protein levels of fra-2 and PARP-1 were increased significantly after light exposure for 12 h (**Figure 1B**). The results indicate that light exposure induced the expression of the fra-2 and PARP-1 proteins in the mice retinas.

Fra-2 overexpression or interference vector transfects to RGC-5 cells

As shown in **Figure 2A**, fra-2 overexpression or interference vectors were inserted in RGC-5 cells. Western blot was performed to detect the fra-2 protein levels in the RGC-5 cells. The results are shown in **Figure 2B**. Fra-2 expression significantly increased in the fra-2 group and decreased in the siFra-2 group.

PARP-1/AIF signal pathway involved in fra-2 induced apoptosis of RGC-5 cells

AnnexinV-FITC/PI flow cytometry assay and MTT were used to evaluate the proliferation and apoptosis of RGC-5 cells. Compared with the control group, the apoptosis of RGC-5 cells was increased significantly in the fra-2 group and decreased significantly in the siFra-2 group (**Figure 3A**). The proliferation of RGC-5 cells in the fra-2 overexpression group was lower than that of the control group, and the proliferation of RGC-5 cells in the siFra-2 group was higher than in the control group (**Figure 3B**).

The protein levels of PARP-1 and AIF were evaluated by Western blot, and the results are shown in **Figure 3C**. Compared with the control group, the protein levels of PARA-1 in the fra-2 group were increased significantly. In the fra-2 group, the protein level of cytosolic AIF in the RGC-5 cells was lower than that of the control group, and the AIF level in the nuclei was higher than that of the control group. We inferred that the overexpression of fra-2 induced apoptosis of the RGC-5 cells might occur via the activation of PARP-1/AIF signaling pathway.

Downregulation of fra-2 can inhibit light-induced RGC-5 cell damage

In order to verify whether Fra-2 is involved in light-induced damage in RGC-5 cells, The RGC-5 cells were divided into a control group, a light exposure group, a fra-2 downexpression + light exposure group (siFra-2 + LE), and a light exposure + NU1025 group (LE + NU1025). An AnnexinV-FITC/PI flow cytometry assay and MTT were used to evaluate the proliferation and apoptosis of the RGC-5 cells. Compared with the control group, the apoptosis of RGC-5 cells in the LE group, the siFra-2 + LE group and the LE + NU1025 group were increased significantly. However, the apoptosis of RGC-5 cells in the siFra-2 + LE and LE + NU1025 groups were lower than that of the LE group (**Figure 4A**). The proliferation of RGC-5 cells in the LE group was lower than that of the control group, but in the siFra-2 + LE and LE + NU1025 groups, the cell proliferation was increased significantly (**Figure 4B**).

As shown in **Figure 4C**, the PARP-1 protein level in the LE group was increased significantly compared to the control group. Light exposure

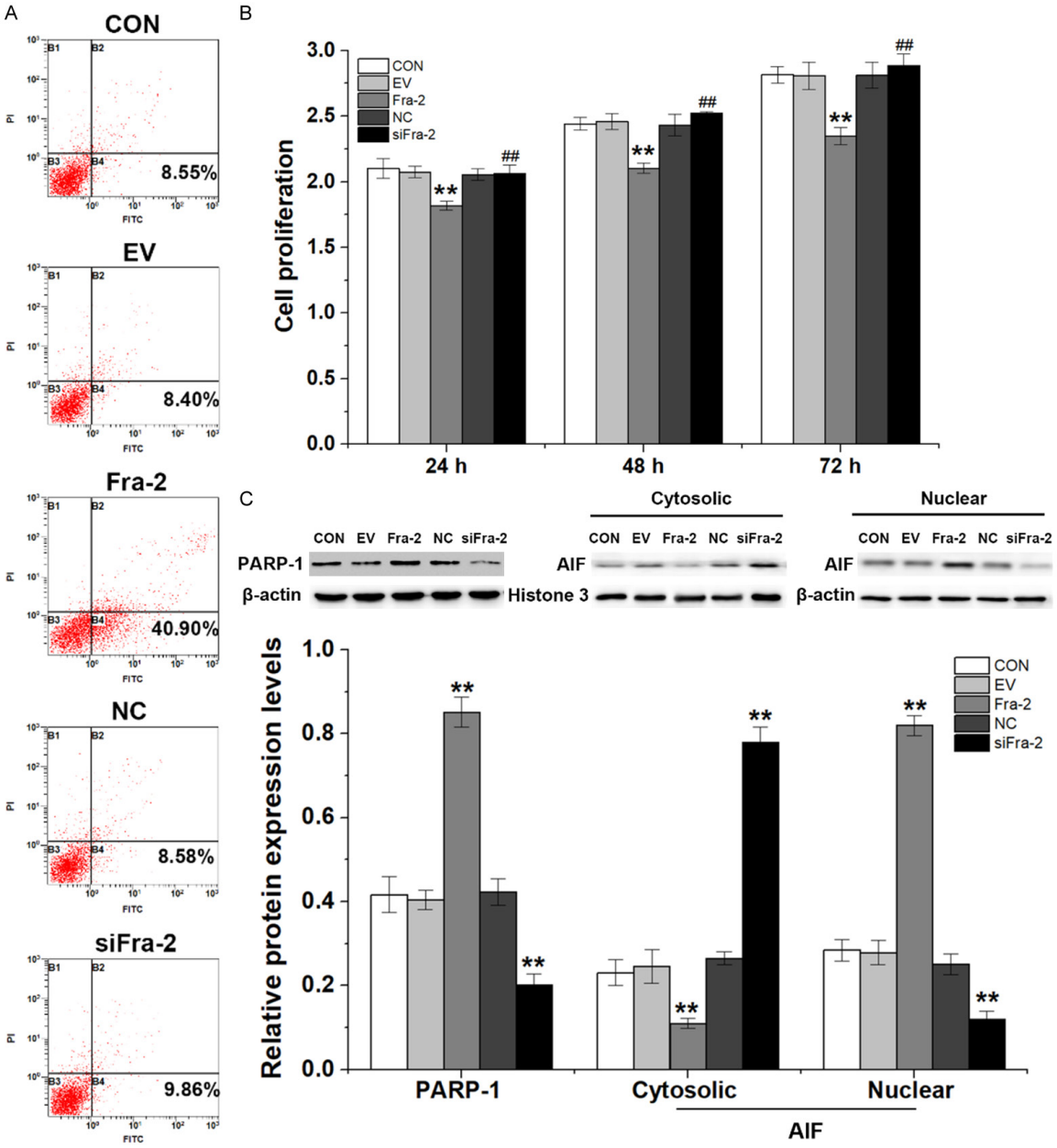

Figure 3. fra-2 affects the apoptosis and proliferation of RGC-5 cells. A. The percentage of apoptotic RGC-5 cells was evaluated by an AnnexinV-FITC/PI flow cytometry assay. B. The proliferation of RGC-5 cells was detected by an MTT assay. C. The protein levels of PARP-1and AIF were detected by western blot. Bands were quantified using Quantity One 5.0 and the fold changes in each protein to β-actin or Histone 3 ratio are shown. Data are shown by means ± SD (n=3); **P<0.01 versus CON group, ##P<0.01 versus Fra-2 group. CON: control group; EV: empty vector; Fra-2: Fra-2 overexpression group; NC: negative group; siFra-2: Fra-2 down-regulation group.

markedly induced the AIF to translocate from the cytoplasms to the nuclei in the RGC-5 cells, which led to caspase-independent chromatinolysis in the nucleus. But in the siFra-2 + LE and LE + NU1025 groups, the PARP-1 protein level was decreased significantly compared with the LE group, and the translocation of AIF from the cytoplasms to the nuclei in the RGC-5 cells was decreased significantly.

Discussion

Recently, evidence has clearly demonstrated that excessive light has a negative effect on the survival of photoreceptors, and, as a consequence, excessive light exposure has been thought to promote the severity of human age-related macular degeneration and to induce some forms of retinitis pigmentosa [8, 27]. In

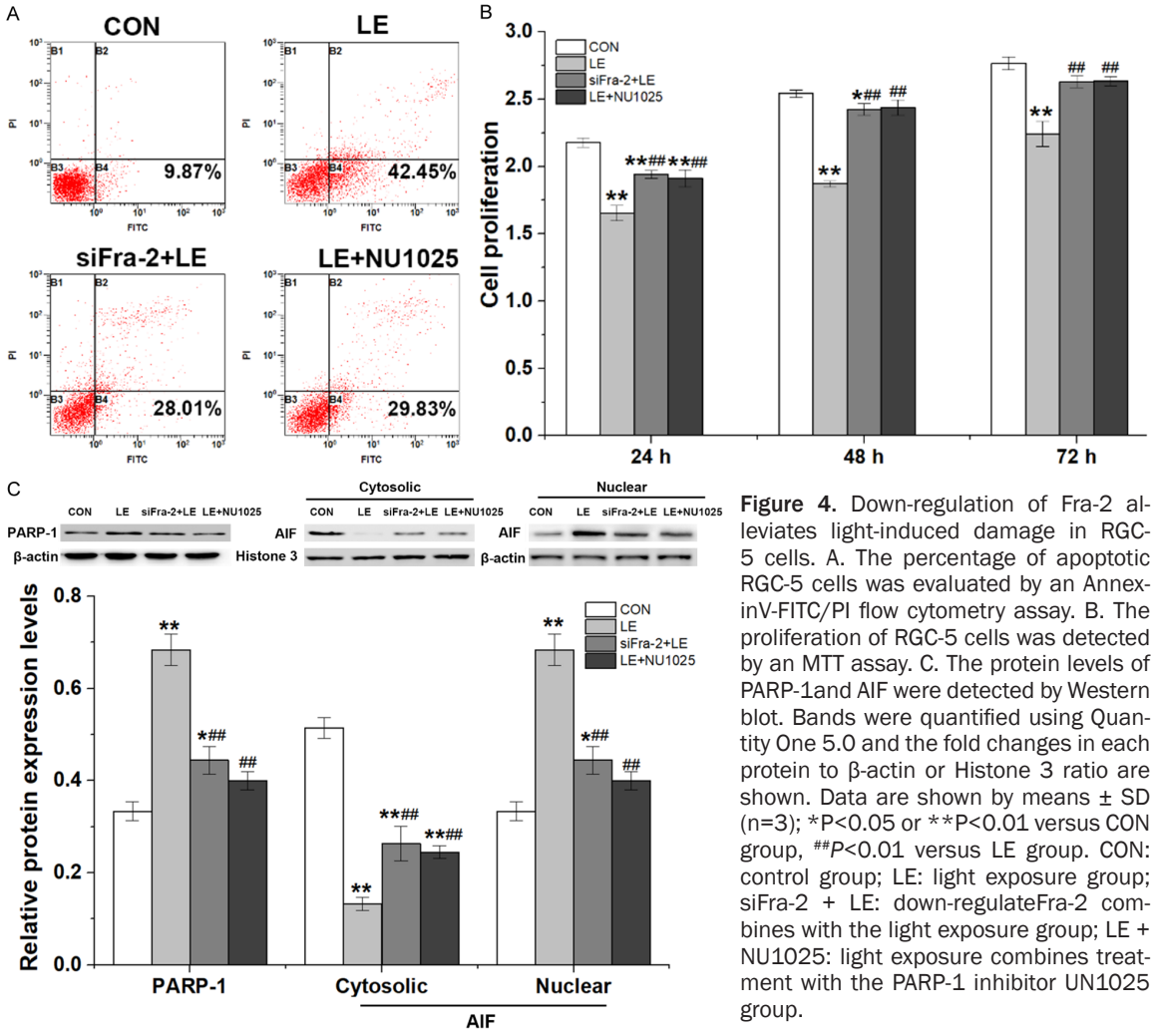

Figure 4. Down-regulation of Fra-2 alleviates light-induced damage in RGC-5 cells. A. The percentage of apoptotic RGC-5 cells was evaluated by an AnnexinV-FITC/PI flow cytometry assay. B. The proliferation of RGC-5 cells was detected by an MTT assay. C. The protein levels of PARP-1and AIF were detected by Western blot. Bands were quantified using Quantity One 5.0 and the fold changes in each protein to β-actin or Histone 3 ratio are shown. Data are shown by means ± SD (n=3); *P<0.05 or **P<0.01 versus CON group, ##P<0.01 versus LE group. CON: control group; LE: light exposure group; siFra-2 + LE: down-regulateFra-2 combines with the light exposure group; LE + NU1025: light exposure combines treatment with the PARP-1 inhibitor UN1025 group.

the present study, mice were exposed from darkness to light with 2600 lux for 36 h that impinged on the retina. Noell et al. recognized that light exposure can induce retinal damage with a photochemical process leading to the generation of reactive oxygen intermediates [28]. In this study, light exposure induced severe retina damage in mice and the up-regulation of fra-2 and PARP-1. Mchenry et al. reported that the overexpression of fra-2 in transgenic mice perturbs normal eye development [29]. However, fra-2 is not involved in light-induced photoreceptor apoptosis because c-fos is more readily activated by light and induces the apoptotic before fra-2 can have any effect in wild-type animals [30, 31]. Therefore, we hypothesized that fra-2 might participate in light induced retina damage by other signaling pathways, such as PARP-1/AIF.

An excessive amount of light exposure can lead to the apoptosis of RGCs in rats [7, 32]. Li et al. demonstrated that direct exposure to visible light causes nuclear DNA damage by activating PARP-1 to trigger death in RGC-5 cells [4]. PARP-1 is well known as nuclear enzyme that repairs DNA damage and is extremely sensitive to various DNA lesions. The nuclear DNA damage can be induced by PARP-1 activation rapidly, and the activity of PARP is increased as much as 500 fold upon binding to breaks in DNA [33, 34]. In the present study, light exposure and overexpressed fra-2 induced the apoptosis and inhibited the proliferation of RGC-5 cells. And the expression of PARP-1 in RGC-5 cells was also increased significantly by light exposure and the up-regulation of fra-2. PARP-1 activation is followed by AIF migration, which is important for caspase-independent apoptotic cell

death. AIF is involved in caspase-independent neuronal cell death by translocating from the mitochondria to the cytosol and nucleus. In this study, AIF was transferred from the cytoplasm to the nucleus by light exposure and overexpression Fra-2 in RGC-5 cells. In addition, the apoptosis of RGC-5 cells was inhibited by down-regulating fra-2 or treating with a RAPA-1 inhibitor. We inferred that fra-2 knockdown might play a protective effect on light exposure induced cell death by inhibiting the AIF transfer to the nucleus thereby blocking PARP-1 activation.

AIF is a mitochondrial enzyme anchored in the inner membrane of the mitochondrial space during normal physiologic conditions. In the induction of cell death, AIF migrates to the nucleus and interacts with DNA and/or RNA which results in caspase-independent chromatin condensation and large-scale DNA fragmentation [35, 36]. In our experiment, we found that that down-regulating fra-2 and treatment with NU1025, a specific inhibitor of PARP-1, was able to partially prevent RGC-5 cell death and increase cell proliferation after light exposure compared with the control group. The process of inhibiting PARP-1 is associated with decreased AIF transfer to the nucleus. These results indicate that PARP-1/AIF signaling pathway is activated by light exposure, and the down-regulation of fra-2 might alleviate light induced cell death by inhibiting the activation of the PARP-1/AIF signaling pathway.

In conclusion, this study indicates that fra-2 is involved in light-induced retinal damage and causes the cell death by activating the PARP-1/AIF signaling pathway. The down-regulation of fra-2 can alleviate light induced retina damage by inhibiting PARP-1-independent AIF release.

Disclosure of conflict of interest

None.

Address correspondence to: Yiqiao Xing, Department of Ophthalmology, Renmin Hospital of Wuhan University, 99 Zhangzhidong Road, Wuhan 430060, Hubei Province, P. R. China. Tel: +86-13707111541; E-mail: yiqiao_xing57@whu.edu.cn

References

[1] Marc RE, Jones BW, Watt CB, Vazquezchona F, Vaughan DK and Organisciak DT. Extreme retinal remodeling triggered by light damage: implications for age related macular degeneration. Mol Vis 2008; 14: 782-806.

[2] Krigel A, Berdugo M, Picard E, Levy-Boukris R, Jaadane I, Jonet L, Dernigoghossian M, Andrieu-Soler C, Torriglia A and Behar-Cohen F. Light-induced retinal damage using different light sources, protocols and rat strains reveals LED phototoxicity. Neuroscience 2016; 339: 296-307.

[3] Izawa H, Shimazawa M, Inoue Y, Uchida S, Moroe H, Tsuruma K and Hara H. Protective effects of NSP-116, a novel imidazolyl aniline derivative, against light-induced retinal damage in vitro and in vivo. Free Radic Biol Med 2016; 96: 304-312.

[4] Li GY, Fan B and Ma TH. Visible light may directly induce nuclear DNA damage triggering the death pathway in RGC-5 cells. Mol Vis 2011; 17: 3279-3289.

[5] Sang A, Xu Y, Jin N, Zhou T, Wang J, Zhu J, Chen C, Shi J, Shuai J, Xu G and Gu Z. Involvement of transcription initiation factor IIB in the light-induced death of rat retinal ganglion cells in vivo. J Mol Histol 2013; 44: 11-18.

[6] Cideciyan AV, Hood DC, Huang Y, Banin E, Li ZY, Stone EM, Milam AH and Jacobson SG. Disease sequence from mutant rhodopsin allele to rod and cone photoreceptor degeneration in man. Proc Natl Acad Sci U S A 1998; 95: 7103-7108.

[7] Marco-Gomariz MA, Hurtado-Montalban N, Vidal-Sanz M, Lund RD and Villegas-Perez MP. Phototoxic-induced photoreceptor degeneration causes retinal ganglion cell degeneration in pigmented rats. J Comp Neurol 2006; 498: 163-179.

[8] Organisciak DT and Vaughan DK. Retinal light damage: mechanisms and protection. Prog Retin Eye Res 2010; 29: 113-134.

[9] García-Ayuso D, Salinas-Navarro M, Agudo M, Cuenca N, Pinilla I, Vidal-Sanz M and Villegas-Pérez MP. Retinal ganglion cell numbers and delayed retinal ganglion cell death in the P23H rat retina. Exp Eye Res 2010; 91: 800-810.

[10] Wang S, Villegas-Perez MP, Holmes T, Lawrence JM, Vidal-Sanz M, Hurtado-Montalban N and Lund RD. Evolving neurovascular relationships in the RCS rat with age. Curr Eye Res 2003; 27: 183-196.

[11] Grimm C, Wenzel A, Hafezi F, Yu S, Redmond TM and Reme CE. Protection of Rpe65-deficient mice identifies rhodopsin as a mediator of light-induced retinal degeneration. Nat Genet 2000; 25: 63-66.

[12] Nishina H, Sato H, Suzuki T, Sato M and Iba H. Isolation and characterization of fra-2, an additional member of the fos gene family. Proc Natl Acad Sci U S A 1990; 87: 3619-3623.

[13] Foletta VC, Sonobe MH, Suzuki T, Endo T, Iba H and Cohen DR. Cloning and characterisation of the mouse fra-2 gene. Oncogene 1994; 9: 3305-3311.
[14] Suzuki T, Okuno H, Yoshida T, Endo T, Nishina H and Iba H. Difference in transcriptional regulatory function between c-Fos and Fra-2. Nucleic Acids Res 1991; 19: 5537-5542.
[15] Skinner M, Qu S, Moore C and Wisdom R. Transcriptional activation and transformation by FosB protein require phosphorylation of the carboxyl-terminal activation domain. Mol Cell Biol 1997; 17: 2372-2380.
[16] Song Y, Song S, Zhang D, Zhang Y, Chen L, Qian L, Shi M, Zhao H, Jiang Z and Guo N. An association of a simultaneous nuclear and cytoplasmic localization of Fra-1 with breast malignancy. BMC Cancer 2006; 6: 298.
[17] Tulchinsky E. Fos family members: regulation, structure and role in oncogenic transformation. Histol Histopathol 2000; 15: 921-928.
[18] Cabon L, Galan-Malo P, Bouharrour A, Delavallee L, Brunelle-Navas MN, Lorenzo HK, Gross A and Susin SA. BID regulates AIF-mediated caspase-independent necroptosis by promoting BAX activation. Cell Death Differ 2012; 19: 245-256.
[19] Boujrad H, Gubkina O, Robert N, Krantic S and Susin SA. AIF-mediated programmed necrosis: a highly regulated way to die. Cell Cycle 2007; 6: 2612-2619.
[20] Li GY and Osborne NN. Oxidative-induced apoptosis to an immortalized ganglion cell line is caspase independent but involves the activation of poly(ADP-ribose)polymerase and apoptosis-inducing factor. Brain Res 2008; 1188: 35-43.
[21] Osborne NN, Li GY, Ji D, Mortiboys HJ and Jackson S. Light affects mitochondria to cause apoptosis to cultured cells: possible relevance to ganglion cell death in certain optic neuropathies. J Neurochem 2008; 105: 2013-2028.
[22] Papeo G, Forte B, Orsini P, Perrera C, Posteri H, Scolaro A and Montagnoli A. Poly(ADP-ribose) polymerase inhibition in cancer therapy: are we close to maturity? Expert Opin Ther Pat 2009; 19: 1377-1400.
[23] Mason KA, Raju U, Buchholz TA, Wang L, Milas ZL and Milas L. Poly (ADP-ribose) polymerase inhibitors in cancer treatment. Am J Clin Oncol 2014; 37: 90-100.
[24] Oplustilova L, Wolanin K, Mistrik M, Korinkova G, Simkova D, Bouchal J, Lenobel R, Bartkova J, Lau A, O'Connor MJ, Lukas J and Bartek J. Evaluation of candidate biomarkers to predict cancer cell sensitivity or resistance to PARP-1 inhibitor treatment. Cell Cycle 2012; 11: 3837-3850.
[25] Lascaratos G, Ji D, Wood JP and Osborne NN. Visible light affects mitochondrial function and induces neuronal death in retinal cell cultures. Vision Res 2007; 47: 1191-1201.
[26] Lascaratos G, Ji D, Wood JP and Osborne NN. Visible light affects mitochondrial function and induces neuronal death in retinal cell cultures. Vision Res 2007; 47: 1191-1201.
[27] Wenzel A, Grimm C, Samardzija M and Reme CE. Molecular mechanisms of light-induced photoreceptor apoptosis and neuroprotection for retinal degeneration. Prog Retin Eye Res 2005; 24: 275-306.
[28] Noell WK, Walker VS, Kang BS and Berman S. Retinal damage by light in rats. Invest Ophthalmol 1966; 5: 450-473.
[29] McHenry JZ, Leon A, Matthaei KI and Cohen DR. Overexpression of fra-2 in transgenic mice perturbs normal eye development. Oncogene 1998; 17: 1131-1140.
[30] Wenzel A, Grimm C, Samardzija M and Reme CE. The genetic modifier Rpe65Leu(450): effect on light damage susceptibility in c-Fos-deficient mice. Invest Ophthalmol Vis Sci 2003; 44: 2798-2802.
[31] Hafezi F, Marti A, Grimm C, Wenzel A and Reme CE. Differential DNA binding activities of the transcription factors AP-1 and Oct-1 during light-induced apoptosis of photoreceptors. Vision Res 1999; 39: 2511-2518.
[32] Sang A, Cheng Y, Lu H, Chen D, Gao R and Shen A. Light-induced retinal ganglion cell damage in vivo involves Dexras1. Mol Vis 2011; 17: 134-143.
[33] Zhang J, Pieper A and Snyder SH. Poly(ADP-ribose) synthetase activation: an early indicator of neurotoxic DNA damage. J Neurochem 1995; 65: 1411-1414.
[34] Menissier-de Murcia J, Molinete M, Gradwohl G, Simonin F and de Murcia G. Zinc-binding domain of poly(ADP-ribose)polymerase participates in the recognition of single strand breaks on DNA. J Mol Biol 1989; 210: 229-233.
[35] Susin SA, Lorenzo HK, Zamzami N, Marzo I, Snow BE, Brothers GM, Mangion J, Jacotot E, Costantini P, Loeffler M, Larochette N, Goodlett DR, Aebersold R, Siderovski DP, Penninger JM and Kroemer G. Molecular characterization of mitochondrial apoptosis-inducing factor. Nature 1999; 397: 441-446.
[36] Ye H, Cande C, Stephanou NC, Jiang S, Gurbuxani S, Larochette N, Daugas E, Garrido C, Kroemer G and Wu H. DNA binding is required for the apoptogenic action of apoptosis inducing factor. Nat Struct Biol 2002; 9: 680-684.