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REVIEW

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A role of Heat Shock Protein 70 in Photoreceptor Cell Death: Potential as a Novel Therapeutic Target in Retinal Degeneration

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SUMMARY

Retinal degenerative diseases (RDs) such as retinitis pigmentosa (RP) are a genetically heterogeneous group of disorders characterized by night blindness and peripheral vision loss, which caused by the dysfunction and death of photoreceptor cells. Although many causative gene mutations have been reported, the final common end stage is photoreceptor cell death. Unfortunately, no effective treatments or therapeutic agents have been discovered. Heat shock protein 70 (HSP70) is highly conserved and has antiapoptotic activities. A few reports have shown that HSP70 plays a role in RDs. Thus, we focused on the role of HSP70 in photoreceptor cell death. Using the *N*-methyl-*N*-nitrosourea (MNU)-induced photoreceptor cell death model in mice, we could examine two stages of the novel cell death mechanism; the early stage, including HSP70 cleavage through protein carbonylation by production of reactive oxygen species, lipid peroxidation and Ca^{2+} influx/calpain activation, and the late stage of cathepsin and/or caspase activation. The upregulation of intact HSP70 expression by its inducer is likely to protect photoreceptor cells. In this review, we focus on the role of HSP70 and the novel cell death signaling process in RDs. We also describe candidate therapeutic agents for RDs.

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Introduction

Retinitis pigmentosa (RP) is one of the major retinal degenerative diseases (RDs), which are caused by photoreceptor cell death [1]. At least 50 million people have these diseases, and no effective drugs have been discovered. Animal models of RP have led to a better understanding of the disease pathology and to the development of therapeutic strategies aimed at curing or slowing down the genetic disorder [2]. It is not easy to choose an appropriate genetic model for RP because there are many causative genes [3]; more than 30 genes and more than 100 rhodopsin mutations are related to RP. Although animal models of RP have a variety of genetic backgrounds (Table 1) [4–30], the final common end stage of RP is photoreceptor cell death.

N-Methyl-*N*-nitrosourea (MNU), an alkylating agent, causes photoreceptor cell loss and significantly decreases the outer nuclear layer thickness within 1 week after intraperitoneal injection [31–33]. MNU selectively damages photoreceptor cells; no other retinal cells are TUNEL positive. Thus, we used the MNU model to study the mechanism of photoreceptor cell death.

Heat shock protein 70 (HSP70) plays an important role in protecting cells against various stresses. However, a few reports have shown the effect of HSP70 on photoreceptor cell death in RDs. In the present review, we describe the role of HSP70 in photoreceptor cell death and discuss the possibility of HSP70 inducers as a new therapeutic tool for RDs.

The Mechanisms of MNU-Induced Photoreceptor Cell Death

Some reports have suggested that MNU induced the generation of free radicals and cell death specifically in retinal photoreceptor cells. Accumulation of 8-hydroxy-deoxyguanosine, an indicator of oxidatively damaged DNA, and 4-hydroxy-2-nonenal (4HNE), a reactive aldehyde species generated endogenously from decomposition of hydroperoxide of ω-6 polyunsaturated fatty acids [34], was detected in MNU-treated mouse retina [33,35]. MNU also causes a decrease in reduced glutathione, which effectively scavenges free radicals and other reactive oxygen species (ROS) [36], leading to an imbalance between the production of ROS and antioxidants.

Intraperitoneal injection of MNU induces the accumulation of intracellular Ca^{2+} in the retina and increases calpain activation, as measured by α-spectrin proteolysis products, which leads to photoreceptor cell death [37,38].

MNU-induced photoreceptor cell loss is caused by a decrease in antiapoptotic Bcl-2 protein, an increase in proapoptotic Bax protein, and the activation of caspase cascades [39,40]. Caspase-3,

Table 1 Genetic models for RP

Animal models		Genotypes	Genes	Site of origin	References
Mice	Natural	Peripherin-rds	Peripherin-rds	Null mutation in the rds/peripherin gene	[4]
		Rd	Peripherin-rds	rd/rd (retinal degeneration) mice	[5]
		Rd-1	PDE6B	Nonsense mutation in exon 7 of the Pde6b gene in all mouse strains with the rd1 mutation	[6]
		Rd-4	–	Inversion encompasses nearly all of Chromosome 4	[7]
		Rd-8	CRB1	Single base deletion in the Crb1 gene	[8]
		Rd-10	PDE6B	Mutation in PDE6b	[9]
		Rd-12	RPE65	Homozygous for the rd12 mutation	[10]
		Rd-16	CEP290	In-frame deletion in a centrosomal protein CEP290	[11]
	Transgenic	307 1-bp del	Peripherin-rds	Single base deletion at codon 307 of the rds-peripherin gene in mice	[12]
		C214S	Peripherin-rds	Peripherin-rds with the C214S (Cys214–>Ser) missense mutation	[13]
		Crx knockout	Cone-rod homeobox	Cone-rod homeobox gene knockout	[14]
		Knockout RPE65	Rhodopsin	Mice that lack the visual pigment rhodopsin (Rpe65-/-)	[15]
		I-255/256	Opsin	Mutant opsin gene with a 3-bp deletion of isoleucine at codon 255/256	[16]
		L185P/Rom-1 null	Peripherin-rds	Doubly heterozygous for a mutation in RDS causing a leucine 185 to proline substitution in rds (L185P) and a null mutation in ROM1	[17]
		MERTK KO	MERTK	Homozygous for a targeted disruption of the Mer receptor tyrosine kinase gene (mer(kd))	[18]
		NMF282	PDE6A	Ethyl nitrosourea (ENU) mutagenesis	[19]
		NMF363	PDE6A	Ethyl nitrosourea (ENU) mutagenesis	[19]
		P216L	Peripherin-rds	Proline 216 to leucine (P216L) amino acid substitution in rds/peripherin	[20]
		P23H	Rhodopsin	Missense mutation (P23H) in the rhodopsin gene	[21]
		P347S	Rhodopsin	Rhodopsin, proline-347 to serine (P347S) mutation	[22]
		Q344ter	Rhodopsin	Heterozygotes with the glutamine-344-to-ter (Q344ter) mutations in the rhodopsin gene (stop codon mutation)	[23]
		Rd12j (NMF137)	PDE6B	Missense point mutation in exon 16 of the beta-subunit of rod phosphodiesterase gene, (PDE6B)	[9]
		$Rpe65^{-/-}$	RPE65	Rpe65-deficient (KO)	[24]
		Sema4A-deficient	Sema4A	Sema4A-deficient	[25]
		Sema4A F350C	Sema4A	Knock-in mouse lines with corresponding mutations (F350C) in the Sema4A gene	[25]
Rat	Natural	RCS	MERTK	Small deletion of RCS DNA that disrupts the gene encoding the receptor tyrosine kinase Mertk	[26]
	Transgenic	P23H	Rhodopsin	Transgenic rat that express P23H rhodopsin	[27]
		S334ter	Rhodopsin	Rhodopsin mutation S334ter	[28]
Chickens	Natural	Rd	GC1	Null mutation in the photoreceptor guanylate cyclase (GC1) gene	[29]
		Rdd	PDE6A	Mutation in PDE6A	[30]

caspase-6, and caspase-8 activities were increased within 3 days after MNU injection.

Although such molecular mechanisms of the MNU-induced photoreceptor cell loss have been described, the total process of the cell death signaling remains obscure. Elucidation of the key molecule that connects these molecular mechanisms is necessary to clarify the photoreceptor cell death signaling process.

Early and Late Stages of MNU-Induced Photoreceptor Cell Death Processes

The HSP70 family is a family of conserved and ubiquitously expressed heat shock proteins. HSP70 is a central component of the cellular network of molecular chaperones and folding catalysts and protects cells from various stresses. Although HSP70 immunoreactivity is localized in the outer nuclear layer and the inner segments of the retina [41], a few studies have reported the role of HSP70 in RDs. Thus, we investigated the role of HSP70 on MNU-induced photoreceptor cell death [33]. Under pathological conditions of neuronal tissues, such as glaucoma and ischemic/reperfusion of the hippocampus, HSP70 is a common substrate of calpain [42]. Carbonylated HSP70 by 4HNE is much more vulnerable to calpain cleavage [43]. We found that the levels of 4HNE were clearly increased in MNU-injected mouse retina. 4HNE is highly reactive and may be considered as a secondary toxic messenger that disseminates and augments initial free radical events [44,45]. Upon the reaction with protein, 4HNE specifically reacts with nucleophilic amino acids, such as cysteine, histidine, and lysine to form their Michael addition adducts possessing carbonyl functionality [46,47]. Thus, HSP70 may be carbonylated by the accumulated 4HNE in MNU-treated mouse retina. In addition, we confirmed that HSP70 was rapidly and calpain-dependently

cleaved after MNU treatment. Our results indicate that HSP70 cleavage might be involved in both oxidative stress and Ca^{2+}/calpain-mediated photoreceptor cell loss. Calpain-mediated cleavage of HSP70 leads to lysosomal rupture and cell death through cathepsin because HSP70 stabilizes lysosomal membranes [48]; this process is known as the calpain–cathepsin hypothesis [49,50]. On the other hand, HSP70 protects against neuronal apoptosis through the inhibition of caspase-dependent apoptosis [51,52]. Thus, caspase-dependent apoptosis occurs in downstream of HSP70 cleavage. Together, our findings suggest that cleavage of HSP70 is a key event that connects the mechanisms of MNU-induced photoreceptor cell death (Figure 1). Focusing on HSP70, the MNU-induced cell death signaling process can be divided into early and late stages. We defined the early stage as HSP70 cleavage through protein carbonylation by oxidative stress, 4HNE production, and Ca^{2+}/calpain activation. The late stage includes the events after HSP70 cleavage, including cathepsin and/or caspase activation.

HSP70 Induction Prevented Photoreceptor Cell Death by MNU

To determine whether HSP70 could protect photoreceptor cell death by MNU, we used valproic acid (VPA), a well-known HSP70 inducer [53]. VPA significantly inhibited MNU-induced retinal thinning and TUNEL-positive photoreceptor cell number through HSP70 induction. Coadministration of VPA and HSP inhibitor abolished the protective effect of HSP70; thus, HSP70 plays a crucial role in the protection of photoreceptor cells. Calpain inhibitor also protects photoreceptor cells because of the suppression of HSP70 cleavage. VPA failed to protect HSP70 from MNU-induced cleavage, but increased the expression levels of intact HSP70. Both VPA and calpain inhibitor completely blocked caspase-3 activation by MNU. In addition, we previously reported that geranylgeranylacetone (GGA), another HSP70 inducer, also attenuated the photoreceptor cell death by MNU through HSP70 induction [33,54]. Thus, inhibition of HSP70 cleavage or induction of intact HSP70 may be possible therapeutic approaches for preventing photoreceptor cell death.

Cytoprotective Effects of HSP70

The photoreceptor cell layer is the primary site of HSP70 synthesis in the retina, and hyperthermia-induced HSP70 in the photoreceptor layer prevents retinal photic injury [55,56]. In the retinal detachment-induced retinal degeneration model, abolishment of HSP70 induction using $HSP70^{-/-}$ mice directly exacerbated photoreceptor apoptosis [57]. Furthermore, HSP990, a HSP70 inducer, enhanced visual function and delayed photoreceptor degeneration in a rhodopsin mutation rat model [58]. These results are in accordance with previous *in vitro* and *in vivo* studies that showed that abolishment of the HSP70 cytoprotective effect augments the initiation of the apoptotic cascade [59–61]. Even in the CNS model, previous studies have reported extensive neuronal damage in $HSP70^{-/-}$ mice after ischemic brain injury, in which the neuronal expression of HSP70 can be regarded as a molecularly defined penumbra of protein denaturation [62]. Thus, HSP70 overexpression directly increased the neuronal viability in various CNS degeneration models [63,64]. These reports showed that HSP70 directly prevented photoreceptor cell death in both genetic RP models and acquired models.

Candidate Therapeutic Agents for RDs

Based on the total image of photoreceptor cell death mechanism that we proposed, protein carbonylation by oxidative stress, Ca^{2+}-dependent protease activation, apoptosis-related molecules, and HSP70 cleavage are involved in MNU-induced photoreceptor cell death. The final common end stage of various pathogenic mechanisms in RDs is photoreceptor cell death. Therefore, protec-

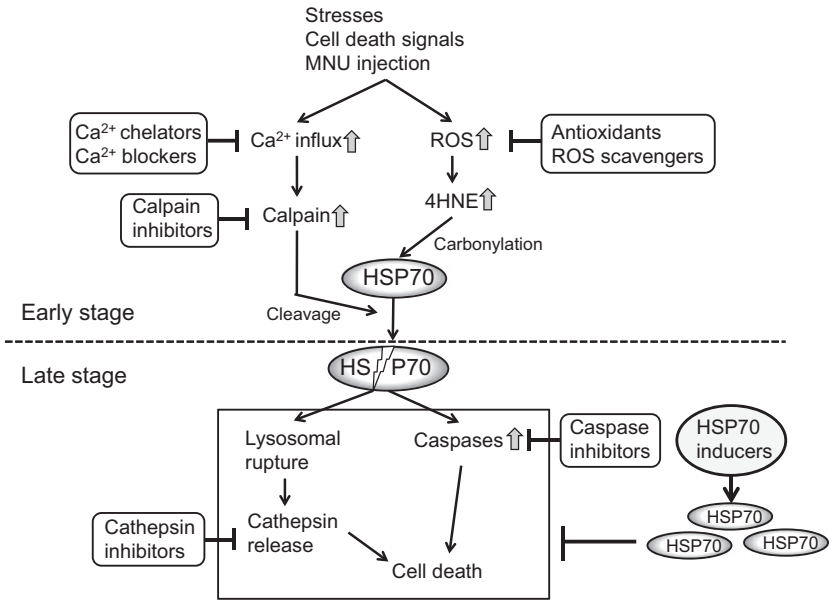

Figure 1 The mechanism of MNU-induced photoreceptor cell death and the candidate therapeutic agents for RDs.

tion of photoreceptor cells may be a useful therapeutic strategy for RDs. Some of the candidate therapeutic agents for RDs are listed in Table 2 [33,35–37,39,54,58,65–121]; these agents include therapeutic agents against the early stage of photoreceptor cell death (antioxidants, ROS scavengers, Ca^{2+} antagonists and calpain inhibitors), therapeutic agents against the late stage of photoreceptor cell death (cathepsin inhibitors and caspase inhibitors), and HSP70 inducers.

As therapeutic agents against the early stage of photoreceptor cell death, antioxidants and ROS scavengers could prevent HSP70 carbonylation through reduction of 4HNE production. In MNU-injected mouse retina, edaravone, a ROS scavenger, can reduce 4HNE generation and the number of TUNEL-positive cells [35]. Polyphenols, such as curcumin and green tea extract, also reduced the number of MNU-induced TUNEL-positive photoreceptor cells [69,71]. The Ca^{2+} antagonist and calpain inhibitors could also protect photoreceptor cells via the inhibition of HSP70 cleavage. Nimodipine, a Ca^{2+} blocker, inhibits MNU-induced photoreceptor cell apoptosis and protects retinal function [36]. A calpain inhibitor, SNJ-1945, restored photoreceptor cell autophagy and photoreceptor cell death in MNU-treated mice [37,38].

Furthermore, as therapeutic agents against the late stage of photoreceptor cell death, both inhibitors of cathepsin and caspases could suppress photoreceptor cell death. Caspase inhibitor was shown to suppress retinal apoptosis in MNU-treated rats [39].

In addition to these existing therapies, we further propose that HSP70 inducers could be novel therapeutic agents to prevent photoreceptor cell death in RDs. Many different chemicals have been reported as HSP70 inducers, including arimoclomol [95], celastrol [100], eupalinolide A/B [102], paeoniflorin [108], and radicicol [111] (Table 2). Drug repositioning is the process of developing new indications for existing drugs or biologics. Some antiulcer agents, such as carbenoxolone [98], polaprezinc [109], and rebamipide [112], induce HSP70 expression in various

Table 2 Candidate therapeutic agents for RDs

Roles	Compounds	References	Roles	Compounds	References
ROS scavenger /Antioxidant	5-S-GAD	[65]	HSP70 inducer	17-AAG	[92]
	Alpha lipoic acid	[66]		17-DMAG	[92]
	Astaxanthin	[67]		2-Cyclopenten-1-one	[93]
	Carnosic acid	[68]		Alkannin	[94]
	Curcumin	[69]		Arimoclomol	[95]
	DHA	[70]		Bicyclol	[96]
	Edaravone	[35]		Bimoclomol	[97]
	Green tea extract	[71]		Carbenoxolone	[98]
	Lutein	[72]		$CdCl_2$	[99]
	Melatonin	[73]		Celastrol	[100]
	N-acetylcysteine	[74]		Curcumin	[101]
	Unoprostone	[75]		Eupalinolide A/B	[102]
				FLZ	[103]
Ca chelator/ /Ca blocker	2-APB	[76]		Geldanamycin	[104]
	BAPTA-AM	[77]		GGA	[54]
	Diltiazem	[78]		Glucuronic acid	[105]
	Flunarizine	[79]		HSP990	[58]
	Nicardipine	[80]		KU-32	[106]
	Nilvadipine	[81]		Linolenic acid	[107]
	Nimodipine	[36]		MG132	[99]
				Paeoniflorin	[108]
Calpain inhibitor	ALLN	[82]		Polaprezinc	[109]
	Calpastatin	[83]		Prostaglandin A1	[110]
	Calpeptin	[77]		Radicicol	[111]
	CYLA	[84]		Rebamipide	[112]
	MDL28170	[85]		Resveratrol	[113]
	MG132	[86]		Safrole oxide	[114]
	PD150606	[82]		Sodium butyrate	[115]
	SJA6017	[87]		Sodium fluoride	[116]
	SNJ-1945	[37]		Sodium salicylate	[117]
				TRC051384	[118]
Cathepsin inhibitor	CA-074Me	[88]		Tributyltin	[119]
	E-64	[89]		VPA	[33]
	Z-FA-FMK	[90]		YC-1	[120]
	Z-FY(t-Bu)-DMK	[91]		Zinc	[121]
Caspases inhibitor	Ac-DEVD-CHO	[39]			

human tissues. Thus, the drug repositioning approach by HSP70 inducers could be an effective way to develop new therapeutic agents for RDs.

Similar Mechanisms of Photoreceptor Cell Death between MNU and RP Models: Early Stage

Although the MNU-induced photoreceptor cell death model is different from the genetic RP model, the two models appear to share similar mechanisms of photoreceptor cell death. The eye has 3- to 4-fold higher oxygen consumption relative to brain tissue and, consequently, has a higher exposure to ROS such as hydrogen peroxide, hydroxyl radicals, and superoxide anions. Oxidative stress is involved in the pathogenesis of a number of diseases including neurodegenerative disorders such as RP [35,122]. Orally administered N-acetylcysteine reduced photoreceptor cell death and preserved cone function by reducing oxidative damage in two models of RP, rd1, and rd10 mice, which have a mutation in the rod photoreceptor-specific cGMP phosphodiesterase (PDE) subunit [74]. In addition, coexpression of superoxide dismutase 2 and catalase in the mitochondria of photoreceptors strongly promotes cell survival and the maintenance of photoreceptor function in rd10 mice [123]. In some RP models, accumulation of 4HNE was detected in photoreceptor cells [124,125]. Therefore, oxidative stress plays a pivotal role in genetic RP models of retinal photoreceptor degradation.

Under pathological conditions, like those in rd1 mice, intracellular Ca^{2+} levels significantly increase in photoreceptor cells, even before the detection of apoptotic cells [126]. Increased photoreceptor cell death in the rd10 mouse retina is associated with Ca^{2+} overload and calpain activation, which both occur prior to signs of cell degeneration [127]. Mitochondrial calpain may activate apoptosis-inducing factor to induce photoreceptor apoptosis in Royal College of Surgeon (RCS) rats, a natural model of recessively inherited RDs that has a disrupted gene for the receptor tyrosine kinase [82,128], and rhodopsin transgenic rats [129]. μ-Calpain contributed to the activation of Bax and apoptosis-inducing factor nuclear translocation in rd1, P23H (missense mutation in the rhodopsin gene), and rhodopsin knockout retinas [130]. The Ca^{2+} antagonist nilvadipine preserved retinal morphology and electroretinogram responses in RCS rats through the upregulation of fibroblast growth factor-2 and antiapoptotic molecules in the retina [131]. A small clinical trial revealed that nilvadipine retarded the progression of central visual field defects in RP [132]. In addition to Ca^{2+} antagonists, calpain inhibitors can attenuate photoreceptor cell death. Mitochondrial μ-calpain inhibitor prevents photoreceptor cell death in RCS rats [128]. In rd1 mice, a highly specific calpain inhibitor, calpastatin, reduced photoreceptor cell death [133]. Therefore, Ca^{2+}-dependent calpain activation may play an important role in RP and even in the MNU-induced photoreceptor cell death model.

Similar Mechanisms of Photoreceptor Cell Death between MNU and RP Models: Late Stage

Cathepsin D also contributed to photoreceptor cell death in rd1, P23H, and rhodopsin knockout retina [130]. Thus, cathepsin inhibitors may attenuate photoreceptor cell death.

In some RP models, altered expression of apoptosis-related proteins was also involved in photoreceptor cell death [134]. Inhibitors of caspase-3, caspase-7, and caspase-9 also showed neuroprotection of photoreceptors at both the structural and functional levels in rhodopsin transgenic rat models of RP [135]. Thus, caspase inhibitors are thought to be effective therapeutic tools for RP.

On the basis of similarities between genetic models of RP and MNU-induced photoreceptor cell death, the therapeutic agents for MNU-induced photoreceptor cell death might be effective in genetic models of RP.

Conclusion

In our recent studies, HSP70 carbonylation by 4HNE and its subsequent cleavage by calpain was one of the novel central mechanisms in photoreceptor cell death. In addition, VPA and GGA protected against photoreceptor cell death by MNU via the induction of HSP70 expression [33,54]. Further studies are needed to confirm these possibilities and to clarify the possible mechanism of pathogenesis and interaction between HSP70 cleavage and chronic photoreceptor cell death using a genetic model for RDs. Taken together, HSP70 inducers may be considered as candidate therapeutic agents for the prevention of RDs, such as RP.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Guadagni V, Novelli E, Piano I, Gargini C, Strettoi E. Pharmacological approaches to retinitis pigmentosa: A laboratory perspective. *Prog Retin Eye Res* 2015;**48**: 62–81.
2. Rivas MA, Vecino E. Animal models and different therapies for treatment of retinitis pigmentosa. *Histol Histopathol* 2009;**24**:1295–1322.
3. Rossmiller B, Mao H, Lewin AS. Gene therapy in animal models of autosomal dominant retinitis pigmentosa. *Mol Vis* 2012;**18**:2479–2496.
4. Cayouette M, Behn D, Sendtner M, Lachapelle P, Gravel C. Intraocular gene transfer of ciliary neurotrophic factor prevents death and increases responsiveness of rod photoreceptors in the retinal degeneration slow mouse. *J Neurosci* 1998;**18**:9282–9293.
5. Bowes C, Li T, Danciger M, Baxter LC, Applebury ML, Farber DB. Retinal degeneration in the rd mouse is caused by a defect in the beta subunit of rod cGMP-phosphodiesterase. *Nature* 1990;**347**:677–680.
6. Paquet-Durand F, Azadi S, Hauck SM, Ueffing M, van Veen T, Ekstrom P. Calpain is activated in degenerating photoreceptors in the rd1 mouse. *J Neurochem* 2006;**96**:802–814.
7. Roderick TH, Chang B, Hawes NL, Heckenlively JR. A new dominant retinal degeneration (Rd4) associated with a chromosomal inversion in the mouse. *Genomics* 1997;**42**:393–396.
8. Mehalow AK, Kameya S, Smith RS, et al. CRB1 is essential for external limiting membrane integrity and photoreceptor morphogenesis in the mammalian retina. *Hum Mol Genet* 2003;**12**:2179–2189.
9. Chang B, Hawes NL, Pardue MT, et al. Two mouse retinal degenerations caused by missense mutations in the beta-subunit of rod cGMP phosphodiesterase gene. *Vision Res* 2007;**47**:624–633.
10. Pang JJ, Chang B, Hawes NL, et al. Retinal degeneration 12 (rd12): A new, spontaneously arising mouse model for human Leber congenital amaurosis (LCA). *Mol Vis* 2005;**11**:152–162.
11. Chang B, Khanna H, Hawes N, et al. In-frame deletion in a novel centrosomal/ciliary protein CEP290/NPHP6 perturbs its interaction with RPGR and results in

early-onset retinal degeneration in the rd16 mouse. *Hum Mol Genet* 2006;**15**:1847–1857.
12. McNally N, Kenna PF, Rancourt D, et al. Murine model of autosomal dominant retinitis pigmentosa generated by targeted deletion at codon 307 of the rds-peripherin gene. *Hum Mol Genet* 2002;**11**:1005–1016.
13. Stricker HM, Ding XQ, Quiambao A, Fliesler SJ, Naash MI. The Cys214–>Ser mutation in peripherin/rds causes a loss-of-function phenotype in transgenic mice. *Biochem J* 2005;**388**:605–613.
14. Watanabe S, Sanuki R, Ueno S, Koyasu T, Hasegawa T, Furukawa T. Tropisms of AAV for subretinal delivery to the neonatal mouse retina and its application for in vivo rescue of developmental photoreceptor disorders. *PLoS ONE* 2013;**8**:e54146.
15. Grimm C, Wenzel A, Hafezi F, Yu S, Redmond TM, Reme CE. Protection of Rpe65-deficient mice identifies rhodopsin as a mediator of light-induced retinal degeneration. *Nat Genet* 2000;**25**:63–66.
16. Penn JS, Li S, Naash MI. Ambient hypoxia reverses retinal vascular attenuation in a transgenic mouse model of autosomal dominant retinitis pigmentosa. *Invest Ophthalmol Vis Sci* 2000;**41**:4007–4013.
17. Kedzierski W, Nusinowitz S, Birch D, et al. Deficiency of rds/peripherin causes photoreceptor death in mouse models of digenic and dominant retinitis pigmentosa. *Proc Natl Acad Sci U S A* 2001;**98**:7718–7723.
18. Duncan JL, LaVail MM, Yasumura D, et al. An RCS-like retinal dystrophy phenotype in mer knockout mice. *Invest Ophthalmol Vis Sci* 2003;**44**:826–838.
19. Sakamoto K, McCluskey M, Wensel TG, Naggert JK, Nishina PM. New mouse models for recessive retinitis pigmentosa caused by mutations in the Pde6a gene. *Hum Mol Genet* 2009;**18**:178–192.
20. Kedzierski W, Lloyd M, Birch DG, Bok D, Travis GH. Generation and analysis of transgenic mice expressing P216L-substituted rds/peripherin in rod photoreceptors. *Invest Ophthalmol Vis Sci* 1997;**38**:498–509.
21. Olsson JE, Gordon JW, Pawlyk BS, et al. Transgenic mice with a rhodopsin mutation (Pro23His): A mouse model of autosomal dominant retinitis pigmentosa. *Neuron* 1992;**9**:815–830.
22. Li T, Snyder WK, Olsson JE, Dryja TP. Transgenic mice carrying the dominant rhodopsin mutation P347S: Evidence for defective vectorial transport of rhodopsin to the outer segments. *Proc Natl Acad Sci U S A* 1996;**93**:14176–14181.
23. Sung CH, Makino C, Baylor D, Nathans J. A rhodopsin gene mutation responsible for autosomal dominant retinitis pigmentosa results in a protein that is defective in localization to the photoreceptor outer segment. *J Neurosci* 1994;**14**:5818–5833.
24. Redmond TM, Yu S, Lee E, et al. Rpe65 is necessary for production of 11-cis-vitamin A in the retinal visual cycle. *Nat Genet* 1998;**20**:344–351.
25. Nojima S, Toyofuku T, Kamao H, et al. A point mutation in Semaphorin 4A associates with defective endosomal sorting and causes retinal degeneration. *Nat Commun* 2013;**4**:1406.
26. D'Cruz PM, Yasumura D, Weir J, et al. Mutation of the receptor tyrosine kinase gene Mertk in the retinal dystrophic RCS rat. *Hum Mol Genet* 2000;**9**:645–651.
27. Machida S, Kondo M, Jamison JA, et al. P23H rhodopsin transgenic rat: Correlation of retinal function with histopathology. *Invest Ophthalmol Vis Sci* 2000;**41**:3200–3209.
28. Green ES, Rendahl KG, Zhou S, et al. Two animal models of retinal degeneration are rescued by recombinant adeno-associated virus-mediated production of FGF-5 and FGF-18. *Mol Ther* 2001;**3**:507–515.
29. Semple-Rowland SL, Lee NR, Van Hooser JP, Palczewski K, Baehr W. A null mutation in the photoreceptor guanylate cyclase gene causes the retinal degeneration chicken phenotype. *Proc Natl Acad Sci U S A* 1998;**95**:1271–1276.
30. Burt DW, Morrice DR, Lester DH, et al. Analysis of the rdd locus in chicken: A model for human retinitis pigmentosa. *Mol Vis* 2003;**9**:164–170.
31. Herrold KM. Pigmentary degeneration of the retina induced by N-methyl-N-nitrosourea. An experimental study in syrian hamsters. *Arch Ophthalmol* 1967;**78**:650–653.
32. Tsubura A, Yoshizawa K, Kuwata M, Uehara N. Animal models for retinitis pigmentosa induced by MNU; disease progression, mechanisms and therapeutic trials. *Histol Histopathol* 2010;**25**:933–944.
33. Koriyama Y, Sugitani K, Ogai K, Kato S. Heat shock protein 70 induction by valproic acid delays photoreceptor cell death by N-methyl-N-nitrosourea in mice. *J Neurochem* 2014;**130**:707–719.
34. Tanito M, Kaidzu S, Anderson RE. Delayed loss of cone and remaining rod photoreceptor cells due to impairment of choroidal circulation after acute light exposure in rats. *Invest Ophthalmol Vis Sci* 2007;**48**:1864–1872.
35. Tsuruma K, Yamauchi M, Inokuchi Y, Sugitani S, Shimazawa M, Hara H. Role of oxidative stress in retinal photoreceptor cell death in N-methyl-N-nitrosourea-treated mice. *J Pharmacol Sci* 2012;**118**:351–362.
36. Wang D, Li Y, Wang Z, Sun GY, Zhang QH. Nimodipine rescues N-methyl-N-nitrosourea-induced retinal degeneration in rats. *Pharmacogn Mag* 2013;**9**:149–154.
37. Oka T, Nakajima T, Tamada Y, Shearer TR, Azuma M. Contribution of calpains to photoreceptor cell death in N-methyl-N-nitrosourea-treated rats. *Exp Neurol* 2007;**204**:39–48.
38. Kuro M, Yoshizawa K, Uehara N, Miki H, Takahashi K, Tsubura A. Calpain inhibition restores basal autophagy and suppresses MNU-induced photoreceptor cell death in mice. *In Vivo* 2011;**25**:617–623.
39. Yoshizawa K, Yang J, Senzaki H, et al. Caspase-3 inhibitor rescues N -methyl- N -nitrosourea-induced retinal degeneration in Sprague-Dawley rats. *Exp Eye Res* 2000;**71**:629–635.
40. Yoshizawa K, Nambu H, Yang J, et al. Mechanisms of photoreceptor cell apoptosis induced by N-methyl-N-nitrosourea in Sprague-Dawley rats. *Lab Invest* 1999;**79**:1359–1367.
41. Dean DO, Kent CR, Tytell M. Constitutive and inducible heat shock protein 70 immunoreactivity in the normal rat eye. *Invest Ophthalmol Vis Sci* 1999;**40**:2952–2962.
42. Nakajima E, David LL, Bystrom C, Shearer TR, Azuma M. Calpain-specific proteolysis in primate retina: Contribution of calpains in cell death. *Invest Ophthalmol Vis Sci* 2006;**47**:5469–5475.
43. Sahara S, Yamashima T. Calpain-mediated Hsp70.1 cleavage in hippocampal CA1 neuronal death. *Biochem Biophys Res Commun* 2010;**393**:806–811.
44. Esterbauer H, Schaur RJ, Zollner H. Chemistry and biochemistry of 4-hydroxynonenal, malonaldehyde and related aldehydes. *Free Radic Biol Med* 1991;**11**:81–128.
45. Uchida K. 4-Hydroxy-2-nonenal: A product and mediator of oxidative stress. *Prog Lipid Res* 2003;**42**:318–343.
46. Shimozu Y, Hirano K, Shibata T, Shibata N, Uchida K. 4-Hydroperoxy-2-nonenal is not just an intermediate but a reactive molecule that covalently modifies proteins to generate unique intramolecular oxidation products. *J Biol Chem* 2011;**286**:29313–29324.
47. Stadtman ER, Berlett BS. Reactive oxygen-mediated protein oxidation in aging and disease. *Drug Metab Rev* 1998;**30**:225–243.
48. Kirkegaard T, Roth AG, Petersen NH, et al. Hsp70 stabilizes lysosomes and reverts Niemann-Pick disease-associated lysosomal pathology. *Nature* 2010;**463**:549–553.
49. Oikawa S, Yamada T, Minohata T, et al. Proteomic identification of carbonylated proteins in the monkey hippocampus after ischemia-reperfusion. *Free Radic Biol Med* 2009;**46**:1472–1477.
50. Yamashima T. Hsp70.1 and related lysosomal factors for necrotic neuronal death. *J Neurochem* 2012;**120**:477–494.
51. Sabirzhanov B, Stoica BA, Hanscom M, Piao CS, Faden AI. Over-expression of HSP70 attenuates caspase-dependent and caspase-independent pathways and inhibits neuronal apoptosis. *J Neurochem* 2012;**123**:542–554.
52. Beere HM, Wolf BB, Cain K, et al. Heat-shock protein 70 inhibits apoptosis by preventing recruitment of procaspase-9 to the Apaf-1 apoptosome. *Nat Cell Biol* 2000;**2**:469–475.
53. Marinova Z, Ren M, Wendland JR, et al. Valproic acid induces functional heat-shock protein 70 via Class I histone deacetylase inhibition in cortical neurons: A potential role of Sp1 acetylation. *J Neurochem* 2009;**111**:976–987.
54. Koriyama Y, Ogai K, Sugitani K, Hisano S, Kato S. Geranylgeranylacetone suppresses N-methyl-N-nitrosourea-induced photoreceptor cell loss in mice. *Adv Exp Med Biol* 2016;**854**:237–243.
55. Tytell M, Barbe MF, Brown IR. Induction of heat shock (stress) protein 70 and its mRNA in the normal and light-damaged rat retina after whole body hyperthermia. *J Neurosci Res* 1994;**38**:19–31.
56. Kim JH, Kim JH, Yu YS, Jeong SM, Kim KW. Protective effect of heat shock proteins 70.1 and 70.3 on retinal photic injury after systemic hyperthermia. *Korean J Ophthalmol* 2005;**19**:116–121.
57. Kayama M, Nakazawa T, Thanos A, et al. Heat shock protein 70 (HSP70) is critical for the photoreceptor stress response after retinal detachment via modulating anti-apoptotic Akt kinase. *Am J Pathol* 2011;**178**:1080–1091.
58. Aguila M, Bevilacqua D, McCulley C, et al. Hsp90 inhibition protects against inherited retinal degeneration. *Hum Mol Genet* 2014;**23**:2164–2175.
59. Spencer JP, Rice-Evans C, Williams RJ. Modulation of pro-survival Akt/protein kinase B and ERK1/2 signaling cascades by quercetin and its in vivo metabolites underlie their action on neuronal viability. *J Biol Chem* 2003;**278**:34783–34793.
60. Sharp FR, Zhan X, Liu DZ. Heat shock proteins in the brain: Role of Hsp70, Hsp 27, and HO-1 (Hsp32) and their therapeutic potential. *Transl Stroke Res* 2013;**4**:685–692.
61. Mansilla MJ, Montalban X, Espejo C. Heat shock protein 70: Roles in multiple sclerosis. *Mol Med* 2012;**18**:1018–1028.
62. Lee SH, Kwon HM, Kim YJ, Lee KM, Kim M, Yoon BW. Effects of hsp70.1 gene knockout on the mitochondrial apoptotic pathway after focal cerebral ischemia. *Stroke* 2004;**35**:2195–2199.
63. Lin PY, Simon SM, Koh WK, Folorunso O, Umbaugh CS, Pierce A. Heat shock factor 1 over-expression protects against exposure of hydrophobic residues on mutant SOD1 and early mortality in a mouse model of amyotrophic lateral sclerosis. *Mol Neurodegener* 2013;**8**:43.
64. Hu D, Chen F, Guan C, Yang F, Qu Y. Anti-hypoxia effect of adenovirus-mediated expression of heat shock protein 70 (HSP70) on primary cultured neurons. *J Neurosci Res* 2013;**91**:1174–1182.
65. Koriyama Y, Ohno M, Kimura T, Kato S. Neuroprotective effects of 5-S-GAD against oxidative stress-induced apoptosis in RGC-5 cells. *Brain Res* 2009;**1296**:187–195.
66. Koriyama Y, Nakayama Y, Matsugo S, Kato S. Protective effect of lipoic acid against oxidative stress is mediated by Keap1/Nrf2-dependent heme oxygenase-1 induction in the RGC-5 cellline. *Brain Res* 2013;**1499**:145–157.

67. Otsuka T, Shimazawa M, Nakanishi T, et al. Protective effects of a dietary carotenoid, astaxanthin, against light-induced retinal damage. *J Pharmacol Sci* 2013;**123**:209–218.
68. Rezaie T, McKercher SR, Kosaka K, et al. Protective effect of carnosic acid, a pro-electrophilic compound, in models of oxidative stress and light-induced retinal degeneration. *Invest Ophthalmol Vis Sci* 2012;**53**:7847–7854.
69. Emoto Y, Yoshizawa K, Uehara N, et al. Curcumin suppresses N-methyl-N-nitrosourea-induced photoreceptor apoptosis in Sprague-Dawley rats. *In Vivo* 2013;**27**:583–590.
70. Bazan NG. Cell survival matters: Docosahexaenoic acid signaling, neuroprotection and photoreceptors. *Trends Neurosci* 2006;**29**:263–271.
71. Emoto Y, Yoshizawa K, Kinoshita Y, et al. Green tea extract suppresses N-methyl-N-nitrosourea-induced photoreceptor apoptosis in Sprague-Dawley rats. *Graefes Arch Clin Exp Ophthalmol* 2014;**252**:1377–1384.
72. Kiang AS, Humphries MM, Campbell M, Humphries P. Antioxidant therapy for retinal disease. *Adv Exp Med Biol* 2014;**801**:783–789.
73. Liang FQ, Aleman TS, Yang Z, Cideciyan AV, Jacobson SG, Bennett J. Melatonin delays photoreceptor degeneration in the rds/rds mouse. *NeuroReport* 2001;**12**:1011–1014.
74. Lee SY, Usui S, Zafar AB, et al. N-Acetylcysteine promotes long-term survival of cones in a model of retinitis pigmentosa. *J Cell Physiol* 2011;**226**:1843–1849.
75. Tsuruma K, Tanaka Y, Shimazawa M, Mashima Y, Hara H. Unoprostone reduces oxidative stress- and light-induced retinal cell death, and phagocytotic dysfunction, by activating BK channels. *Mol Vis* 2011;**17**:3556–3565.
76. Li J, Wang P, Yu S, Zheng Z, Xu X. Calcium entry mediates hyperglycemia-induced apoptosis through Ca (2 +)/calmodulin-dependent kinase II in retinal capillary endothelial cells. *Mol Vis* 2012;**18**:2371–2379.
77. Kim C, Yun N, Lee YM, et al. Gel-based protease proteomics for identifying the novel calpain substrates in dopaminergic neuronal cell. *J Biol Chem* 2013;**288**:36717–36732.
78. Frasson M, Sahel JA, Fabre M, Simonutti M, Dreyfus H, Picaud S. Retinitis pigmentosa: Rod photoreceptor rescue by a calcium-channel blocker in the rd mouse. *Nat Med* 1999;**5**:1183–1187.
79. Edward DP, Lam TT, Shahinfar S, Li J, Tso MO. Amelioration of light-induced retinal degeneration by a calcium overload blocker. Flunarizine. *Arch Ophthalmol* 1991;**109**:554–562.
80. Takano Y, Ohguro H, Dezawa M, et al. Study of drug effects of calcium channel blockers on retinal degeneration of rd mouse. *Biochem Biophys Res Commun* 2004;**313**:1015–1022.
81. Yamazaki H, Ohguro H, Maeda T, et al. Preservation of retinal morphology and functions in royal college surgeons rat by nilvadipine, a Ca(2 +) antagonist. *Invest Ophthalmol Vis Sci* 2002;**43**:919–926.
82. Mizukoshi S, Nakazawa M, Sato K, Ozaki T, Metoki T, Ishiguro S. Activation of mitochondrial calpain and release of apoptosis-inducing factor from mitochondria in RCS rat retinal degeneration. *Exp Eye Res* 2010;**91**:353–361.
83. Yang J, Weimer RM, Kallop D, et al. Regulation of axon degeneration after injury and in development by the endogenous calpain inhibitor calpastatin. *Neuron* 2013;**80**:1175–1189.
84. David J, Melamud A, Kesner L, et al. A novel calpain inhibitor for treatment of transient retinal ischemia in the rat. *NeuroReport* 2011;**22**:633–636.
85. Lee E, Eom JE, Kim HL, et al. Neuroprotective effect of undecylenic acid extracted from Ricinus communis L. through inhibition of mu-calpain. *Eur J Pharm Sci* 2012;**46**:17–25.
86. Tie L, Xu Y, Lin YH, et al. Down-regulation of brain-pancreas relative protein in diabetic rats and by high glucose in PC12 cells: Prevention by calpain inhibitors. *J Pharmacol Sci* 2008;**106**:28–37.
87. Sharma AK, Rohrer B. Calcium-induced calpain mediates apoptosis via caspase-3 in a mouse photoreceptor cell line. *J Biol Chem* 2004;**279**:35564–35572.
88. Cho K, Yoon SY, Choi JE, Kang HJ, Jang HY, Kim DH. CA-074Me, a cathepsin B inhibitor, decreases APP accumulation and protects primary rat cortical neurons treated with okadaic acid. *Neurosci Lett* 2013;**548**:222–227.
89. Okubo A, Sameshima M, Unoki K, Uehara F, Bird AC. Ultrastructural changes associated with accumulation of inclusion bodies in rat retinal pigment epithelium. *Invest Ophthalmol Vis Sci* 2000;**41**:4305–4312.
90. Gottron FJ, Ying HS, Choi DW. Caspase inhibition selectively reduces the apoptotic component of oxygen-glucose deprivation-induced cortical neuronal cell death. *Mol Cell Neurosci* 1997;**9**:159–169.
91. Xiang B, Fei X, Zhuang W, Fang Y, Qin Z, Liang Z. Cathepsin L is involved in 6-hydroxydopamine induced apoptosis of SH-SY5Y neuroblastoma cells. *Brain Res* 2011;**1387**:29–38.
92. Turturici G, Sconzo G, Geraci F. Hsp70 and its molecular role in nervous system diseases. *Biochem Res Int* 2011;**2011**:618127.
93. Rossi A, Elia G, Santoro MG. 2-Cyclopenten-1-one, a new inducer of heat shock protein 70 with antiviral activity. *J Biol Chem* 1996;**271**:32192–32196.
94. Yoshihisa Y, Hassan MA, Furusawa Y, Tabuchi Y, Kondo T, Shimizu T. Alkannin, HSP70 inducer, protects against UVB-induced apoptosis in human keratinocytes. *PLoS ONE* 2012;**7**:e47903.
95. Parfitt DA, Aguila M, McCulley CH, et al. The heat-shock response co-inducer arimoclomol protects against retinal degeneration in rhodopsin retinitis pigmentosa. *Cell Death Dis* 2014;**5**:e1236.
96. Bao XQ, Liu GT. Induction of overexpression of the 27- and 70-kDa heat shock proteins by bicyclol attenuates concanavalin A-Induced liver injury through suppression of nuclear factor-kappaB in mice. *Mol Pharmacol* 2009;**75**:1180–1188.
97. Hargitai J, Lewis H, Boros I, et al. Bimoclomol, a heat shock protein co-inducer, acts by the prolonged activation of heat shock factor-1. *Biochem Biophys Res Commun* 2003;**307**:689–695.
98. Nagayama S, Jono H, Suzaki H, et al. Carbenoxolone, a new inducer of heat shock protein 70. *Life Sci* 2001;**69**:2867–2873.
99. Wang T, Yu Q, Chen J, Deng B, Qian L, Le Y. PP2A mediated AMPK inhibition promotes HSP70 expression in heat shock response. *PLoS ONE* 2010;**5**:e13096.
100. Kyung H, Kwong JM, Bekerman V, et al. Celastrol supports survival of retinal ganglion cells injured by optic nerve crush. *Brain Res* 2015;**1609**:21–30.
101. Xia C, Cai Y, Li S, Yang J, Xiao G. Curcumin increases HSP70 expression in primary rat cortical neuronal apoptosis induced by gp120 V3 loop peptide. *Neurochem Res* 2015;**40**:1996–2005.
102. Yamashita Y, Ikeda T, Matsuda M, Maji D, Hoshino T, Mizushima T. Purification and characterization of HSP-inducers from Eupatorium lindleyanum. *Biochem Pharmacol* 2012;**83**:909–922.
103. Kong XC, Zhang D, Qian C, Liu GT, Bao XQ. FLZ, a novel HSP27 and HSP70 inducer, protects SH-SY5Y cells from apoptosis caused by MPP(+). *Brain Res* 2011;**1383**:99–107.
104. Lu A, Ran R, Parmentier-Batteur S, Nee A, Sharp FR. Geldanamycin induces heat shock proteins in brain and protects against focal cerebral ischemia. *J Neurochem* 2002;**81**:355–364.
105. Kim YM, Kim HJ, Song EJ, Lee KJ. Glucuronic acid is a novel inducer of heat shock response. *Mol Cell Biochem* 2004;**259**:23–33.
106. Li C, Ma J, Zhao H, Blagg BS, Dobrowsky RT. Induction of heat shock protein 70 (Hsp70) prevents neuregulin-induced demyelination by enhancing the proteasomal clearance of c-Jun. *ASN Neuro* 2012;**4**:e00102.
107. Blondeau N, Widmann C, Lazdunski M, Heurteaux C. Polyunsaturated fatty acids induce ischemic and epileptic tolerance. *Neuroscience* 2002;**109**:231–241.
108. Yan D, Saito K, Ohmi Y, Fujie N, Ohtsuka K. Paeoniflorin, a novel heat shock protein-inducing compound. *Cell Stress Chaperones* 2004;**9**:378–389.
109. Odashima M, Otaka M, Jin M, et al. Induction of a 72-kDa heat-shock protein in cultured rat gastric mucosal cells and rat gastric mucosa by zinc L-carnosine. *Dig Dis Sci* 2002;**47**:2799–2804.
110. Wang X, Qin ZH, Leng Y, et al. Prostaglandin A1 inhibits rotenone-induced apoptosis in SH-SY5Y cells. *J Neurochem* 2002;**83**:1094–1102.
111. Miyabara EH, Martin JL, Griffin TM, Moriscot AS, Mestril R. Overexpression of inducible 70-kDa heat shock protein in mouse attenuates skeletal muscle damage induced by cryolesioning. *Am J Physiol Cell Physiol* 2006;**290**:C1128–C1138.
112. Hahm KB, Park IS, Kim YS, et al. Role of rebamipide on induction of heat-shock proteins and protection against reactive oxygen metabolite-mediated cell damage in cultured gastric mucosal cells. *Free Radic Biol Med* 1997;**22**:711–716.
113. Putics A, Vegh EM, Csermely P, Soti C. Resveratrol induces the heat-shock response and protects human cells from severe heat stress. *Antioxid Redox Signal* 2008;**10**:65–75.
114. Zhao Y, Xin J, Sun C, Zhao B, Zhao J, Su L. Safrole oxide induced neuronal differentiation of rat bone-marrow mesenchymal stem cells by elevating Hsp70. *Gene* 2012;**509**:85–92.
115. Garcia-Bermejo L, Vilaboa NE, Perez C, Galan A, De Blas E, Aller P. Modulation of heat-shock protein 70 (HSP70) gene expression by sodium butyrate in U-937 promonocytic cells: Relationships with differentiation and apoptosis. *Exp Cell Res* 1997;**236**:268–274.
116. Cheng TJ, Chen TM, Chen CH, Lai YK. Induction of stress response and differential expression of 70 kDa stress proteins by sodium fluoride in HeLa and rat brain tumor 9L cells. *J Cell Biochem* 1998;**69**:221–231.
117. Ishihara K, Horiguchi K, Yamagishi N, Hatayama T. Identification of sodium salicylate as an hsp inducer using a simple screening system for stress response modulators in mammalian cells. *Eur J Biochem* 2003;**270**:3461–3468.
118. Mohanan A, Deshpande S, Jamadarkhana PG, et al. Delayed intervention in experimental stroke with TRC051384–a small molecule HSP70 inducer. *Neuropharmacology* 2011;**60**:991–999.
119. Zhang H, Liu AY. Tributyltin is a potent inducer of the heat shock response in human diploid fibroblasts. *J Cell Physiol* 1992;**153**:460–466.
120. Liu YN, Pan SL, Peng CY, et al. YC-1 induces heat shock protein 70 expression and prevents oxidized LDL-mediated apoptosis in vascular smooth muscle cells. *Shock* 2008;**30**:274–279.
121. Cheng Y, Liu YF, Liang J. Protective effect of zinc: A potent heat shock protein inducer in cold preservation of rat liver. *Hepatobiliary Pancreat Dis Int* 2002;**1**:258–261.
122. Murakami Y, Ikeda Y, Yoshida N, et al. MutT homolog-1 attenuates oxidative DNA damage and delays photoreceptor cell death in inherited retinal degeneration. *Am J Pathol* 2012;**181**:1378–1386.
123. Usui S, Komeima K, Lee SY, et al. Increased expression of catalase and superoxide dismutase 2 reduces cone cell death in retinitis pigmentosa. *Mol Ther* 2009;**17**:778–786.

124. Shen J, Yang X, Dong A, et al. Oxidative damage is a potential cause of cone cell death in retinitis pigmentosa. *J Cell Physiol* 2005;**203**:457–464.
125. Tanito M, Haniu H, Elliott MH, Singh AK, Matsumoto H, Anderson RE. Identification of 4-hydroxynonenal-modified retinal proteins induced by photooxidative stress prior to retinal degeneration. *Free Radic Biol Med* 2006;**41**:1847–1859.
126. Doonan F, Donovan M, Cotter TG. Activation of multiple pathways during photoreceptor apoptosis in the rd mouse. *Invest Ophthalmol Vis Sci* 2005;**46**:3530–3538.
127. Rodriguez-Muela N, Hernandez-Pinto AM, Serrano-Puebla A, et al. Lysosomal membrane permeabilization and autophagy blockade contribute to photoreceptor cell death in a mouse model of retinitis pigmentosa. *Cell Death Differ* 2015;**22**:476–487.
128. Ozaki T, Nakazawa M, Yamashita T, et al. Intravitreal injection or topical eye-drop application of a mu-calpain C2L domain peptide protects against photoreceptor cell death in Royal College of Surgeons' rats, a model of retinitis pigmentosa. *Biochim Biophys Acta* 2012;**1822**:1783–1795.
129. Ozaki T, Ishiguro S, Hirano S, et al. Inhibitory peptide of mitochondrial mu-calpain protects against photoreceptor degeneration in rhodopsin transgenic S334ter and P23H rats. *PLoS ONE* 2013;**8**:e71650.
130. Comitato A, Sanges D, Rossi A, Humphries MM, Marigo V. Activation of Bax in three models of retinitis pigmentosa. *Invest Ophthalmol Vis Sci* 2014;**55**:3555–3562.
131. Sato M, Ohguro H, Ohguro I, et al. Study of pharmacological effects of nilvadipine on RCS rat retinal degeneration by microarray analysis. *Biochem Biophys Res Commun* 2003;**306**:826–831.
132. Nakazawa M, Ohguro H, Takeuchi K, Miyagawa Y, Ito T, Metoki T. Effect of nilvadipine on central visual field in retinitis pigmentosa: A 30-month clinical trial. *Ophthalmologica* 2011;**225**:120–126.
133. Paquet-Durand F, Sanges D, McCall J, et al. Photoreceptor rescue and toxicity induced by different calpain inhibitors. *J Neurochem* 2010;**115**:930–940.
134. Sizova OS, Shinde VM, Lenox AR, Gorbatyuk MS. Modulation of cellular signaling pathways in P23H rhodopsin photoreceptors. *Cell Signal* 2014;**26**:665–672.
135. Leonard KC, Petrin D, Coupland SG, et al. XIAP protection of photoreceptors in animal models of retinitis pigmentosa. *PLoS ONE* 2007;**2**:e314.

