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Adaptive Plasticity in the Retina: Protection Against Acute Injury and Neurodegenerative Disease by Conditioning Stimuli

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Abstract

Although both preclinical and clinical conditioning studies in heart and brain lead the field of conditioning medicine, investigations of retinal conditioning still number more than 100. In this brief review, we highlight findings to date from animal and cell culture models of conditioning that provide demonstrated protection in acute and chronic retinal injury and disease models. The multitude of stimuli used to condition the retina, the signaling mediators and pathways identified, and the injury- and disease-resilient phenotypes documented are discussed herein, along with our recommendations for the kinds of studies needed to continue to advance this promising field. In our view, the robust protection afforded by these adaptive epigenetic responses to conditioning stress provides significant incentives for both furthering our investment in bench research and underwriting clinical trials, so that the full potential of this therapy can be realized.

Visual impairment and blindness exact huge tolls on the health and economy of Western societies and across the world (Pascolini and Mariotti, 2012; Chan et al., 2017). Although advances in gene- and cell-based therapies raise hope as therapeutic options, treatments for many of these diseases remain largely elusive – particularly those designed to directly protect retinal neurons, glia, and vasculature. Because the retina has its embryologic origin in the same ectoderm layer that forms all central nervous system tissues, some insights gained from the many lines of investigation into endogenous neuroprotection of the brain may well be applicable to the retina. Indeed, many studies focused on conditioning triggers and retinal signaling pathways mediating adaptive responses to ocular injury parallel those published in brain, but for the most part, they pale in quantity and quality. That said, innovative, well-designed studies of retinal conditioning may also reveal mechanisms and therapeutic strategies relevant to brain disorders.

The purpose of the present review is to highlight a number of acute and chronic retinal pathologies in animal models in which a variety of physiologic and pharmacologic conditioning approaches have proven efficacious, including more recent postconditioning studies. Signaling pathways and other mechanistic findings relevant to the observed pathology will be discussed, as well as the salient features of the respective disease-resilient phenotypes. Finally, we will share our perspectives on the kinds of basic and translational investigations needed to achieve bench-to-bedside successes for such a promising therapy.

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Preclinical models of retinal injury and conditioning-based protection

Historical perspective

The first paper that revealed endogenous neuroprotection in retina was published in Science in 1988 (Barbe et al., 1988), very close to the time that the fields of cardiac (Murry et al., 1986) and brain (Kitagawa et al., 1991) conditioning were birthed. In this seminal study, the extent of bright light-induced photoreceptor degeneration in the rat retina was decreased if animals were exposed earlier to heat shock. However, despite being at the starting line about the same time, and despite the unique accessibility of the retina as an experimental model, the field of retinal conditioning has lagged considerably behind those of cardiac and cerebral conditioning ever since. Studies in the latter disciplines advanced to clinical trials many years ago, whereas in ophthalmology even the most exciting of findings at the bench have not led to any published or even registered human studies. Some of this difference is certainly the result of broad dissimilarities in the prevalence of the respective diseases, which in turn lead to greater numbers of clinical trials of conditioning in myocardial infarction and stroke relative to those for retinal ischemia or phototoxic injury. Still, promising research opportunities exist but have yet to be captured. Moreover, there are several powerful, noninvasive retinal structure/function measures available to ophthalmologists that could be employed serially in both acute and chronic disease studies to quantify conditioning-mediated improvements in function and recovery kinetics that simply have no equivalent match for the neurologist and cardiologist.

Injury models

Save for a couple of studies from one lab using hamsters (Liu et al., 2013; Liu et al., 2017), and one using zebrafish (Tucker et al., 2011), in vivo preclinical studies of retinal conditioning published to date have been conducted in either rats or mice. *In vitro* investigations using cultured primary or immortalized retinal ganglion cells (Brandt et al., 2011), photoreceptors (Tanito et al., 2007; Yi et al., 2012), and retinal pigment epithelial cells (Gao and Talalay, 2004; Tanito et al., 2005; Sharma et al., 2009) have been conducted, as have studies in the isolated optic nerve (Hamner et al., 2015), but collectively these are few in number. With respect to acute retinal injury, ischemia represents the primary injury used in retinal conditioning studies (>60 papers), typically induced by elevating intraocular pressure above systolic for 30–60 min, or by intravitreal delivery of glutamate, or by oxygen-glucose deprivation in vitro (Table 1). Retinal phototoxicity represents the second most common acute injury model in the field (>25 papers) (Table 1). A small number of studies have been published using oxidative stress as the injurious stimulus, or intravitreal TNFα (Table 1). Animal models of glaucoma and diabetes have been used to examine the potential for inducing long-lasting adaptive conditioning responses in the setting of chronic retinal disease, including some studies in genetic models of retinal degeneration (Table 1). Finally, some studies have crushed or transected the optic nerve as models for assessing efficacy of conditioning treatments in glaucoma or axonal injury (Table 1).

Conditioning stimuli

As documented in other tissues, an amazingly wide variety of distinct conditioning stimuli trigger adaptive responses in the retina, all of which generally afford significant resilience to

acute ischemic and phototoxic injury, and also to chronic retinal injury associated with glaucoma, diabetes, etc. This robust diversity underscores a well-accepted feature of conditioning in virtually all tissues: a redundancy or parallelism in proximal signaling mechanisms that ultimately converge on a common set of epigenetic regulators and transcription factors; the latter activate a relatively conserved genomic response that gives rise to the protective phenotype. At first blush, this plethora of activators might seem to bode well for identifying potential molecular targets for conditioning therapeutics, but in fact this has not been the case, in part because some stimuli are simply too risk-fraught to be amenable to clinical translation, and also because of the fundamental challenge associated with dose titration, particularly in human subjects, a population that is nowhere near as homogeneous as teenage male rodents.

A brief period of noninjurious retinal ischemia is the most common conditioning stimulus used to induce retinal resilience (>45 papers) (Table 2), generally against injury caused by longer periods of ischemia, but also against phototoxic injury (Casson et al., 2003), and glaucoma (Belforte et al., 2011)). Similarly, periods of noninjurious cyclic light and red light precondition against more severe phototoxic injury, and also against oxidative stress-induced injury (Table 2). From a translational and drug development viewpoint, as well as a mechanistic one, it is instructive to subdivide conditioning stimuli that are “physiologic” and involve exposure of the entire animal from those physiologic stimuli directed at the eye, as well as from specific pharmacologic challenges. Examples of physiologic conditioning stimuli that show efficacy in studies of retinal injury/disease include (Table 2): a single or intermittent exposure to hypoxia, hyperoxia, a variety of inhaled gases (argon, carbon monoxide, hydrogen, and hydrogen sulfide), hyperthermia and hypothermia, γ-radiation, brief unilateral carotid occlusion, exercise, dietary changes, exposure to enriched environments, and remote conditioning. The aforementioned ‘physiologic’ stimuli were systemic, which raises questions about humoral factor cross-tolerance, ‘cumulative’ tissue effects, changes in metabolic status, etc. However, protection was also afforded by locally-directed physiologic stimuli, such as (Table 2): transcorneal electrical stimulation, γ-radiation, hypothermia, intravitreal LPS, the TLR4 agonist prothymosin-α, and “photobiomodulation”, wherein 670-nm red light is directed at the eye.

Pharmacologic treatments, administered systemically, that proved efficacious for retinal conditioning include (Table 2): the K-ATP channel agonist diazoxide, the volatile gas anesthetic sevoflurane, zinc, hypoxia-inducible factor-1α (HIF-1α) stabilizers, erythropoietin, and sulforaphane. Intravitreally or topically applied agents that conditioned the retina against injury also include the K-ATP channel agonist diazoxide, as well as leukemia inhibitory factor (LIF), low-dose N-methyl-D-aspartate (NMDA), the ER stress inducer tunicamycin, and media from mesenchymal stem cells (Dreixler et al., 2014); in the case of the latter, even more robust protection is achieved using media from hypoxic-preconditioned mesenchymal stem cells.

As with other tissues, cross-tolerance – the protection against one type of injury induced by conditioning with a different type of stimulus – also holds true in retina (Table 3). Thus, single or repetitive exposures to hypoxia, the hypoxia-inducible factor mimetics cobalt or deferroxamine, K-ATP channel openers, carbon monoxide, hydrogen, argon, hydrogen

sulfide, sulforaphane, heat stress, hypothermia, LPS and Toll-like receptor agonists, and remote conditioning can condition against retinal ischemic injury. More protracted conditions such as environmental enrichment, ketogenic diets, intermittent fasting, flavonoid-supplemented diets, and exercise also protect against retinal ischemia. Similarly, phototoxic injury is attenuated in animals conditioned with brief ischemia, hypoxia, hyperoxia, heat stress, electrical stimulation, HIF-1α overexpression, erythropoietin, sulforaphane, pyruvate, LIF, LPS, remote conditioning, and exercise. Examples of conceptually similar cross-tolerance to other types of retinal injury achieved by challenging the animal with a stress stimulus quite distinct from the injury itself include protection against glaucomatous injury by intermittent hypoxia or ischemia, radiation, zinc, heat stress, and dietary interventions, as well as protection against diabetic retinopathy by intermittent brief ischemia, exercise, and environmental enrichment. Finally, retinal ganglion cell (RGC) death following optic nerve crush or transection is attenuated by carbon monoxide, hyperbaric oxygen, and remote conditioning.

Protecting against acute injury versus chronic retinal disease

Another important distinction worthy of underscoring is conditioning against acute retinal injuries versus conditioning against chronic retinal neurodegenerative diseases. As alluded to earlier, the majority of retinal conditioning studies involve ischemic or phototoxic injury, in which many retinal cells undergo a relatively rapid, apoptotic cell death process. Typically, a single preconditioning or postconditioning stimulus is sufficient to trigger a transient neuroprotective response that abrogates these injuries if these treatments occur shortly before or shortly after the acute injury. However, a longstanding question is whether such an adaptive response could ever be leveraged therapeutically in the case of more chronic diseases wherein the rate of cell death is slow and protracted (over years in humans). Accumulating evidence indicates that repetitive conditioning may sustain the adaptive phenotype (Gidday, 2015a), and thus provide a therapeutic strategy for enhancing resilience against the more mild but progressive demise of retinal cell populations in diseases like glaucoma, diabetic retinopathy, and retinitis pigmentosa. For example, intermittent hypoxia, administered prior to (Zhu et al., 2012) or following (Gidday, 2015b) intraocular pressure elevation in a mouse model of glaucoma afforded protection of RGC soma and axons, as did intermittent brief ischemia in a rat model of glaucoma (Belforte et al., 2011). Similarly, intermittent brief ischemia is an efficacious intervention to prevent, or halt, the functional demise of the retina in diabetes (Fernandez et al., 2011; Fernandez et al., 2012; Salido et al., 2013b), as is (intermittent) exercise (Kim et al., 2013), and, interestingly, rearing animals in an enriched environment (Dorfman et al., 2014). Voluntary exercise reduced photoreceptor loss and improved visual acuity in the rd10 genetic model of inherited retinal degeneration (Hanif et al., 2015). Clearly, more research in this exciting area is warranted, and may in fact set the stage for similar investigations in other neurodegenerative diseases in the CNS.

Preconditioning and postconditioning

The vast majority of studies on retinal conditioning utilized a preconditioning approach to triggering innate mechanisms of neuroprotection. While valuable for demonstrating the extent to which the induction of endogenous mechanisms can provide resilience to injury and disease, there remain valid concerns about clinical applicability and relevance because

of the transience of the protective phenotype so induced. Although this approach has potential benefit for certain elective ophthalmologic surgeries wherein preconditioning could be intentionally administered, in most cases one cannot predict when an acute retinal injurious event will occur. However, as with the fields of cardiac and cerebral conditioning, the discovery that postconditioning may also stimulate innate adaptive responses of significant magnitude provides rich opportunities for further preclinical examination, with the hope that, at some future time, such bench-to-bedside applications may be feasible. Mechanistically, at least with respect to brief ischemia as the stimulus, the protection afforded by preconditioning is not additive with that afforded by postconditioning (Dreixler et al., 2010), suggesting that postconditioning may induce similar adaptive responses without the need for pretreatment. Finally, in the case of chronic retinal disease, postconditioning often takes the form of an ongoing series of repetitive conditioning stimuli administered during disease progression, – i.e., “per”-conditioning rather than “post”-conditioning may be the most apt semantic in these instances (Gidday, 2015b)). These studies support further exploration of the possibility of augmenting innate resilience to chronic disease and slowing the kinetics of retinal degeneration.

Retinal postconditioning studies are compiled in Table 4. To date, those using single or multiple short-duration ischemic challenges are the most common. Studies compiled in Table 4 demonstrate that this stimulus is protective against ischemia- and diabetes-induced injury. Brief, postischemic exposures to argon, carbon monoxide, and hydrogen gas also promote protection against ischemic injury, as do intravitreal delivery of stem cell-conditioned media, remote ischemic conditioning of the leg, and postischemic recovery in an enriched environment. Enriched environment housing during disease progression also lessens retinal pathology in diabetic rats. Phototoxic injury is reduced by pyruvate and red light photobiomodulation, and protection against glaucomatous injury is afforded by intermittent hypoxia, intermittent heat shock, and intermittent zinc. In addition, post-injury exposure to carbon monoxide attenuates apoptotic RGC loss secondary to optic nerve crush. Studies have demonstrated neuroprotective efficacy following the “late” (24 h or more after injury) application of conditioning stimuli (Dreixler et al., 2011c; Dreixler et al., 2014; Roth et al., 2016), and others have shown that conditioning initiated well into diabetes (Salido et al., 2013b; Dorfman et al., 2014) or glaucoma (Inman et al., 2013) still slows or even halts further progression of the pathology. These are provocative findings that should further raise translational excitement, and more per- and post-conditioning studies are warranted to fully explore the potential of this therapeutic approach.

Signaling Mediators

Many studies have attempted to elucidate the molecular pathways responsible for signaling the response to a given preconditioning stimulus. In response to brief conditioning ischemia in rats (prior to the injurious insult), studies report increased levels of the following: basic fibroblast growth factor (bFGF) (Casson et al., 2003); the alpha (Ding et al., 2009), delta (Dreixler et al., 2008), epsilon (Dreixler et al., 2008), and gamma (Ding et al., 2009) isoforms of protein kinase-C (PKC); ERK1/2 (Zhang et al., 2002; Dreixler et al., 2009b; Dreixler et al., 2011b); p38 MAPK (Zhang et al., 2002; Dreixler et al., 2009a; Dreixler et al., 2011b); Akt/protein kinase B (Dreixler et al., 2009c); mitogen-activated protein kinase

phosphatase-1 (MKP-1) (Dreixler et al., 2011b); glial fibrillary acidic protein (GFAP) (Casson et al., 2003); erythropoietin (EPO) receptors (Dreixler et al., 2009b); vascular endothelial growth factor-A (VEGF-A) (Nishijima et al., 2007); heat shock protein-27 (HSP27) (Li et al., 2003); and autophagy-like apg3 mRNA (Wu et al., 2006). Intravitreal, low-dose NMDA as a preconditioning stimulus increases heat shock transcriptional factor (HSF) -1 and -2 expression (Ahn et al., 2008) and HSP72 expression (Kwong et al., 2003; Ahn et al., 2008). Increases in LIF expression are triggered by bright cyclic light preconditioning (Chollangi et al., 2009; Lange et al., 2010; Chrenek et al., 2016) and exercise (Chrenek et al., 2016). In fact, a metabolomics study revealed that preconditioning light stress causes a significant reorganization of lipid metabolism and changes in amino acid composition (de la Barca et al., 2017). Hypoxic preconditioning also increases LIF expression (Lange et al., 2010), as well as delta opioid receptors (Peng et al., 2009), and of course HIF-1α (Zhu et al., 2007; Ueki et al., 2008). Levels of bFGF and ciliary neurotrophic factor (CNTF) (Liu et al., 1998), as well as thioredoxin and thioredoxin reductase (Tanito et al., 2007) occur after bright cyclic light preconditioning, as does the nuclear translocation of the transcription factor Nrf2 (Tanito et al., 2007). In terms of gaseous preconditioning stimuli, hydrogen sulfide preconditioning increased expression of HSP90, NFkB, c-jun terminal kinase (JNK), and ERK1/2 (Biermann et al., 2011), whereas carbon monoxide increased phosphorylated p38 expression, and the DNA binding activity of the transcription factor CREB (Biermann et al., 2010). Not surprisingly, heat stress led to the induction of HSP 64, HSP74, and HSP110 (Barbe et al., 1988) and HSP72 within RGCs (Park et al., 2001).

With respect to signaling activity induced by pharmacologic preconditioning stimuli, the efficacy of which implies causal roles for their endogenous equivalents, preconditioning with mitochondrial K-ATP receptor openers involves PKC (Roth, 2004; Dreixler et al., 2008), p38 (Dreixler et al., 2009a), and constitutive NOS activity (Roth, 2004). K-ATP channels are also implicated in adenosine-mediated conditioning, as is PKC (Li et al., 2000). Preconditioning with intravitreal LIF resulted in sustained elevations in signal transducer and activator of transcription-3 (STAT3) in all retina cells, and ERK1/2 in Müller cells (Ueki et al., 2008). Preconditioning with the TLR4 agonist prothymosin-alpha caused mild activation, proliferation, and migration of microglia (Halder et al., 2015). TLR4 receptor activation by LPS preconditioning was also associated with increased retinal NOS activity (Franco et al., 2008), as well as pAkt expression (Bordone et al., 2012), and the proliferation and migration of retinal microglia (Halder et al., 2013). In photoreceptor cultures, LPS decreased the expression of tumor necrosis factor-α (TNFα) and its receptors TNFR1 and TNFR2 (Yi et al., 2012). The hypoxia-mimetic cobalt chloride increased glucose transporter-1 and -3 expression in retinal homogenates and in isolated vessels (Badr et al., 1999) upregulated HSP27 expression in cultured retinal neurons and in vivo retina (Whitlock et al., 2005), and increased heme oxygenase-1 expression and activity (Peng et al., 2011). Similarly, increased HIF-1α and adrenomedullin expression were confirmed to follow preconditioning with the hypoxia-mimetic deferroxamine (Zhu et al., 2008). Finally, zinc preconditioning induced HSP72 expression in RGCs (Park et al., 2001).

Regarding signaling mediators involved in diet- and exercise-induced retinal protection, α-lipoic acid supplementation increased several antioxidant indices in the DBA/2J retina

(Inman et al., 2013). Sulforaphane increased thioredoxin levels *in vivo*, and in retinal pigment epithelium (RPE) cultures, induced binding of Nrf2 to the anti-oxidant response element of the thioredoxin gene (Tanito et al., 2005). Based on the ability of a TrkB receptor antagonist to block its cytoprotective effects in two models of photoreceptor degeneration, exercise promotes beneficial increases in retinal brain-derived neurotrophic factor (BDNF) expression (Lawson et al., 2014; Hanif et al., 2015).

While the aforementioned investigations provide some valuable insights into the proximal signaling mechanisms underlying preconditioning-induced retinal protection from injury/disease, analyses of changes in gene expression in response to a given conditioning stimulus, and ultimately the protein profile that defines the injury- or disease-resistant phenotype provide a distinct perspective on resilience mechanisms.

Resilient Genotypes/Phenotypes

Although changes in gene expression do not necessarily predict changes in protein profiles in a 1:1 manner, they can still provide insightful mechanistic clues as to the conditioning-induced, injury-resilient proteome. As examples, in the initial hours to days following a brief period of retinal ischemic preconditioning in the rat, a significant overrepresentation of genes involved in amino-acyl-tRNA synthetase activity and amino acid transport has been measured, both of which were downregulated relative to sham controls (Kamphuis et al., 2007b). Decreases in tRNA aminoacylation-related genes, and increases in immune-related and anti-apoptotic genes were also measured following ischemia in the preconditioned retinae (Kamphuis et al., 2007a). These paired findings imply that reductions in translational activity and in turn reductions in protein synthetic metabolism may represent a fundamental response to preconditioning, a hypothesis that also anchors the cerebral conditioning field (Simon, 2016). Similar transcriptomics-based analyses following hypoxic preconditioning in mice implicate adrenomedullin and paraoxonase-1 as participating in establishing the neuroprotection (Thiersch et al., 2008). Unique gene signatures induced by photobiomodulation with red light, or dietary saffron, were revealed by rat retina microarrays, including an overall downregulation of noncoding RNAs (Natoli et al., 2010). In vitro, sulfophorane preconditioning of human adult RPE cell cultures induced “phase 2” genes (glutathione, NAD(P)H:quinone oxidoreductase, heme oxygenase, thioredoxin, etc.) (Gao and Talalay, 2004)), suggestive of a strongly anti-oxidant phenotype.

On the one hand, retinal neurons, glia, and vascular cells of the normal, resting tissue respond epigenetically to preconditioning stimuli with a pan-resilient phenotype, not ‘knowing’ what particular injury or disease may ultimately befall them. Thus, increases in anti-inflammatory, anti-oxidant, and anti-apoptotic ‘tone’ and overall upregulation of survival mechanisms are not unexpected. On the other hand, in the setting of chronic disease, and also with postconditioning, retinal cells are integrating the conditioning stimulus into a new or ongoing pathologic context, so the resultant responses may indeed be influenced by, or perhaps tailored to, that specific injury or disease. At any rate, a collective registration of experimentally observed phenotypes – beyond the various functional and morphologic endpoints used to document resilience – is useful for understanding the larger context of adaptive resilience, as well as for identifying potential therapeutic targets.

Specifically, retinae protected from ischemia secondary to pre- and post-conditioning exhibit the following postischemic phenotypes relative to nonconditioned animals (Table 5): With respect to anti-apoptotic endpoints, studies report reduced caspase-3 expression/activity, reduced caspase-3 and caspase-2 cleavage, decreased expression of PARP and bax, and increased Bcl-2 expression. Reductions in astrocytic GFAP expression, reductions in microglial activation, and reductions in immigration of proliferative microglia and macrophages into retina are reported anti-inflammatory characteristics, as well as reductions in leukocyte rolling and accumulation, and lower levels of IL-1β and TNFα. A number of anti-oxidative stress phenotypes have been reported, including increased nuclear Nrf2 translocation/expression, and increased heme oxygenase-1 expression. Metabolic phenotypes include increased glutamate uptake and glutamine synthetase activity, improved mitochondrial oxidative phosphorylation enzyme activity, increased HSP90 expression, and less ionic dysregulation. For signaling intermediates, the resilient retina exhibited decreased NFkB phosphorylation and DNA binding, and decreased p38 and JNK phosphorylation. The status of ERK1/2 phosphorylation is controversial, with some reporting increases and others decreases. Epigenetic endpoints measured include lower levels of Class-1 HDAC activity (less postischemic hypoacetylation), decreased histone protein H2B, and increased histone proteins H2B, H3, and H4 and the polycomb group protein RING. Finally, the resilient retina exhibits less ischemia-induced hypoperfusion.

Phototoxicity-resilient phenotypic features include (Table 5): reduced microglial influx in outer retina, lower levels of Müller cell GFAP expression and other stress markers, reductions in lipid peroxidation and its breakdown product acrolein, reductions in the mitochondrial bax/cytoplasmic bax ratio and in caspase-1 activation, and higher levels of BDNF, HSPs, and STAT3 in photoreceptors.

In models of glaucoma, conditioning interventions resulted in the following phenotypes (Table 5): Elevated HSP72 expression, increased levels of the antioxidants ceruloplasmin and heme oxygenase-1, and reductions in lipid peroxidation. In addition, improvements in anterograde and retrograde transport function have been measured. Finally, less microglial activation occurs early in disease, and the extent of monocyte entry into the optic nerve head is reduced as well.

Conditioning animals to treat advancing diabetes results in the following phenotypes: Vascular leakage is reduced, perhaps directly secondary to lower levels of VEGF. Regarding inflammation, treatment maintains GFAP expression in astrocytes, but lowers it in Müller cells; TNFα levels are also reduced. Lower levels of oxidative stress are evidenced by reductions in lipid peroxidation indices and maintained catalase activity. Finally, treated animals maintain levels of glutamine synthetase activity, BDNF, and pAkt (all of which decrease in untreated cohorts), exhibit increases in bcl-2 and decreases in bax expression, and show improvements in anterograde transport.

Correlation is not Causation

It is important to keep in mind that measuring changes in any number of signaling mediators, transcription factors, and even phenotypes made in conjunction with a functional

or histological metric of cell death/protection only provides correlative evidence of the former's involvement. If a given conditioning intervention leads to retinal protection in a particular injury/disease setting, then it would not be unexpected to find higher levels of beneficial, pro-survival molecules and lower levels of pro-inflammatory, pro-free radical, and pro-apoptotic molecules than in nonconditioned controls. However, such findings do not necessarily allow one to claim that conditioning-induced protection resulted from these same changes, which is unfortunately a common conclusion of not only retina-focused but other conditioning studies as well. Rather, causative evidence for a given mechanism, whether using an in vivo or *in vitro* model, can only be forthcoming from studies that employ pharmacologic antagonists, antisense oligos, siRNAs, and genetic interventions (assuming each of these interventions exhibits the expected specificity and efficacy). Given this criterion, below is a brief outline of the molecules causally identified as participating in the mediation of the retinal adaptive response to pre- and/or post-conditioning.

With respect to mechanisms involved in the protection against retinal ischemia, causal studies implicate the involvement of p38 (Dreixler et al., 2009a; Dreixler et al., 2011a), MKP-1 (Dreixler et al., 2011b), protein kinase C isoforms (Li et al., 2000; Sakamoto et al., 2004; Dreixler et al., 2008), K-ATP channels (Li et al., 2000; Ettaiche et al. (2001); Sakamoto et al., 2001; Sakamoto et al., 2004), pAkt isoforms (Dreixler et al., 2009c; Dreixler et al., 2011a), EPO (Junk et al., 2002; Dreixler et al., 2009b), vascular endothelial growth factor-A (VEGF-A) (Nishijima et al., 2007), heme oxygenase-1 (Peng et al., 2011), A1 and A2a adenosine receptors (Li and Roth, 1999; Li et al., 2000; Nonaka et al., 2001; Sakamoto et al., 2001; Sakamoto et al., 2004), opioid receptors (Husain et al., 2009), LIF receptors (Chollangi et al., 2009), TLR4 receptors (Halder et al., 2015), and both constitutive (Zhu et al., 2006) and inducible (Lin and Roth, 1999) isoforms of nitric oxide synthase. The abrogation of exercise-induced protection against phototoxicity by a BDNF TrkB receptor antagonist implicates BDNF signaling in mediating this protective effect (Lawson et al., 2014). Causal evidence for the involvement of Nrf2-ARE pathway in the bright cyclic light-mediated protection against phototoxicity in mouse photoreceptor-derived 661W cells has also been provided (Tanito et al., 2007).

Regarding the leveraging of mutant mice to yield causal insights into conditioning mechanisms, the reduction in preconditioning-mediated protection of photoreceptors in photoreceptor-specific gp130-null mice, but not in Müller cell-specific gp130-null mice, provides strong support for the requirement for this signal transducing receptor in auto-protecting photoreceptors against phototoxicity (Ueki et al., 2009). The dependency of brief ischemic conditioning of the optic nerve against severe ischemia on innate immune cell signaling pathways and microglial-specific expression of type 1 interferon receptor (IFNAR1) is reflected by impaired protection in Toll-like receptor-4 (TRL4)-null mice, IFNAR1-null mice, and mice with microglial-targeted IFNAR1 deletion (Hamner et al., 2015). That prothymosin-alpha preconditioning acts through TLR4 receptors to protect against retinal ischemia was confirmed using TLR4-null mice (Halder et al., 2015).

Many of the studies involving genetic manipulations as a strategy to interrogate mechanisms of retinal conditioning have focused on the transcription factor HIF-1α. Given their landmark study that photoreceptor damage by bright light could be abrogated by hypoxic

preconditioning (Grimm et al., 2002), the Grimm laboratory then set about providing causal evidence for HIF-1α involvement. However, despite knocking out HIF-1α in photoreceptors (Thiersch et al., 2009)), or knocking out both HIF-1α and HIF-2α in rods or HIF-2α only in rods (Kast et al., 2016)), hypoxic conditioning-induced photoreceptor protection from phototoxicity remained intact. These findings indicate that either paracrine mediators released from other HIF-1α–containing retinal cells contribute to photoreceptor protection and/or hypoxia exerts HIF-1α–independent protective effects within rods. The latter possibility is additionally supported by the finding that genetically stabilizing HIF-1α expression in rods under normoxic, baseline conditions is protective, although not to the extent afforded by hypoxic preconditioning (Lange et al., 2011). A similar conclusion implicating intercellularly-acting mediators and/or HIF-1α-independent cytoprotective mechanisms was advanced for RGCs, when knocking out HIF-1α in these cells did not adversely affect the ability of hypoxic preconditioning to protect them from glaucomatous injury (Zhu et al., 2013). Finally, despite being strongly induced in response to hypoxic preconditioning, knockout studies demonstrated that the HIF-1α target gene cyclin-dependent kinase inhibitor-1a (p21) was not essential for the induction of photoreceptor bright light resilience (Thiersch et al., 2008).

Gap Analysis/Future Directions

Overall, the preclinical data defining this field indicate that the success of conditioning-mediated protection has earned this treatment strategy a seat at the table, both in terms of garnering government and foundational support for furthering bench studies as well as for initiating clinical trials. After all, the evidence suggests such interventions may someday provide a low-cost, safe, and potentially very efficacious means of treatment – features that one might consider as defining an ideal therapeutic. While continuing to amass robust results in animals will help maintain momentum, efforts are needed to “get the word out”, and to implement advocacy strategies that promote recognition of the potential of adaptive epigenetics-based therapeutics among retinal disease funding stakeholders and clinicians alike. Most accept at face value the concept that cocktail treatments that operate mechanistically at multiple levels of pathobiology and across multiple cell types are better than monotherapies targeting a single molecule or receptor on a single cell. Surprisingly, however, few ophthalmologists even know this bench-proven treatment modality exists or are aware that clinical trials could be initiated tomorrow, in theory.

As alluded to earlier, save for studies of neurodegenerative disease, publications in the field of conditioning for acute retinal injury lag considerably behind those in cerebral and cardiac conditioning, so, in one sense, additional contributions of any kind would be welcome. That said, there is the possibility to ‘cut to the chase’ by prioritizing the following kinds of studies: For one, more preclinical studies should incorporate functional outcome measures, and rely less on histological endpoints. Measures made at longer post-injury timepoints are also desirable, to ensure that the protection observed early after injury is sustained, and not simply delayed. Investigations of how changes in retinal vascular endothelial cells, smooth muscle cells, Müller cells, optic nerve astrocytes, microglia, and other retinal cells respond to conditioning and exhibit cell-specific resilience would help balance the current, predominantly neuron-centric findings that define our current understanding. Studies of

potential gender-dependencies are needed. Similarly, studies of conditioning in aged animals, and in animals with co-morbidities (hypertension, diabetes, obesity, etc.), would help move the field in a translational direction, as would studies in higher mammals. More attention to conditioning-induced protection of axons, relevant to glaucoma and other retinal diseases, is also desirable; in that context, the effects of conditioning on RGC axon regeneration, integration, and synaptic reconnection metrics have yet to be investigated. Given the limited clinical opportunities for preconditioning vis-à-vis the demonstrated preclinical efficacy of postconditioning for acute injuries (Fernandez et al., 2009b; Fernandez et al., 2009a; Dreixler et al., 2010; Dreixler et al., 2011c; Dreixler et al., 2011a; Ren et al., 2011; Albarracin and Valter, 2012; Schallner et al., 2012; Zhang et al., 2014; Ulbrich et al., 2015; Wang et al., 2016) and per-conditioning for chronic retinal degenerative diseases (Park et al., 2001; Fernandez et al., 2011; Fernandez et al., 2012; Salido et al., 2013b; Gidday, 2015b; Chen et al., 2016), we urge more investigations along these lines. More ‘rescue’ studies, wherein the kinetics of advancing neurodegenerative disease are altered by initiating treatment well into the disease course (Inman et al., 2013; Salido et al., 2013b; Dorfman et al., 2014), would also help fuel translational interest.

Other factors carry legitimate weight in deciding how best to move forward. For example, it is probably unnecessary to posit that we need to understand every mechanistic detail before moving forward with clinical trials; Phase I safety trials could be initiated for demonstrably safe stimuli that promote reproducible protection in our animal models, as has occurred in the aforementioned companion fields of cerebral and cardiac conditioning. Mechanism-focused studies still have merit and may indeed play crucial roles in identifying molecular targets for pharmacological conditioning. In this regard, more investigations of epigenetic regulatory pathways might be especially fruitful. Translational relevance would be enhanced by animal testing of conditioning stimuli that exhibit a high safety profile, unlike brief ischemia, LPS, carbon monoxide, hyperthermia, or excitotoxins, which will never find traction in the clinic as therapeutics. Given the beneficial effects observed in animals that lifestyle variables like exercise (Kim et al., 2013; Chrysostomou et al., 2014; Lawson et al., 2014; Hanif et al., 2015) and dietary interventions (Natoli et al., 2010; Kong et al., 2012; Zarnowski et al., 2012; Inman et al., 2013; Patel et al., 2015) can exert on resistance to retinal injury/disease, an easy argument can also be made for encouraging more of these kinds of chronic conditioning-like investigations. It might also be instructive to consider the overall incidence of morbidity resulting from retinal injury and disease, and focus more preclinical effort on those injuries and diseases wherein an efficacious conditioning-based therapy can have the greatest societal impact. In all instances, more long-term benefits for the field will accrue from following proper lab practices with respect to study design, randomization, a priori power analyses and defined inclusion/exclusion criteria, transparency, blinding, rigor/reproducibility, and appropriate statistical analyses.

Clinical trials of conditioning for protection of the heart and brain predominantly involve remote conditioning of a limb; sensing this future, at least three companies have designed programmable cuffs to automatically administer the intermittent ischemia protocol on the human arm or leg. Thus, more preclinical studies designed to explore the efficacy of remote cuff conditioning for protecting the retina against acute and chronic injury would provide the foundational support that will ultimately be necessary for advancing this particular treatment

modality to patients with retinal injury/disease. Three studies (Liu et al., 2013; Zhang et al., 2014; Brandli et al., 2016) have set the precedent. On the other hand, it may be premature to completely rule out the clinical use of hypoxia (Grimm et al., 2002; Zhu et al., 2002; Zhu et al., 2007; Berkowitz et al., 2008; Peng et al., 2009; Zhu et al., 2012; Gidday, 2015b), hydrogen sulfide (Biermann et al., 2011), volatile anesthetics (Szabadfi et al., 2012), cyclic bright light (Li et al., 2001; Tanito et al., 2007; Chollangi et al., 2009; Ueki et al., 2009; Zhu et al., 2010; Chrenek et al., 2016) or red light (Natoli et al., 2010; Albarracin and Valter, 2012) as a conditioning stimulus. The same can be said for considering a 'safe' pharmacologic approach (Ettaiche et al., 2001; Junk et al., 2002; Tanito et al., 2005; Ren et al., 2011; Pan et al., 2014). Although specificity is advantageous if one molecule or receptor, acting proximally in the signal transduction cascade, can be targeted therapeutically to drive the entire adaptive response, systemic-level physiologic stimuli like remote conditioning may be worth prioritizing if the tradeoff is efficacy over specificity, and peripheral side effects, if any, are shown to be minimal. Certainly remote conditioning earns points for ease of application.

No matter what the conditioning stimulus, dose titration remains one of the key bench-to-bedside challenges. Postconditioning against an acute retinal injury may seem simple in theory, but efficacy may be significantly influenced by gender, age and other comorbid conditions. Postconditioning or per-conditioning during advancing neurodegenerative disease raises key questions with respect to identifying the ideal frequency of the repetitive conditioning stimulus that precludes habituation and circumvents potentially progressive side effects. These concerns, in turn, bring to the forefront the dire need for conditioning biomarkers that can reflect the safety and efficacy of a given treatment dose, as well as biomarkers that can reveal in a confirmatory way the achievement or ongoing maintenance of a resilient phenotype. The former would be of tremendous value in titrating or calibrating 'personalized medicine' conditioning treatments for each patient, taking into account differences in age, gender, co-morbid disease, existing medications, etc. Having indirect or direct readouts of a disease-resilient retinal phenotype would have value in optimizing outcomes of elective surgical cases, as well as in defining therapeutic windows and guiding dosing protocols in cases of chronic ocular pathology.

Conclusions

Although not putting up comparable parallels to the explosion in experimental and clinical studies that define the cardiac and cerebral conditioning fields since their advent about 3 decades ago, the field of retinal resilience to acute injury and chronic disease has advanced at a respectable rate and features many notable, elegant, high-quality studies. In fact, although small in number, there are more investigations exploring – and demonstrating efficacy in – repetitive conditioning-based therapies for chronic neurodegenerative diseases of the retina than there are for chronic diseases of the heart and brain. Nevertheless, concerted efforts supporting new and ongoing investments of financial and personnel resources are desperately needed in this corner of the ophthalmologic R&D enterprise, given its broad and deep potential to significantly reduce visual morbidity across the globe.

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Table 1

Injury Models

Retinal Ischemia	Roth et al., 1998; Li and Roth, 1999; Lin and Roth, 1999; Li et al., 2000; Nishiyama et al., 2000; Ettaiche et al., 2001; Nonaka et al., 2001; Sakamoto et al., 2001; Junk et al., 2002; Zhang et al., 2002; Zhu et al., 2002; Li et al., 2003; Sakamoto et al., 2004; Whitlock et al., 2005; Roth et al., 2006; Wu et al., 2006; Zhu et al., 2006; Kamphuis et al., 2007a; Kamphuis et al., 2007b; Nishijima et al., 2007; Zhu et al., 2007; Berkowitz et al., 2008; Dreixler et al., 2008; Franco et al., 2008; Zhu, 2008; Dreixler et al., 2009a; Dreixler et al., 2009b; Dreixler et al., 2009c; Fernandez et al., 2009a; Fernandez et al., 2009b; Husain et al., 2009; Peng et al., 2009; Biermann et al., 2010; Dreixler et al., 2010; Stowell et al., 2010; Biermann et al., 2011; Dreixler et al., 2011b; Dreixler et al., 2011c; Dreixler et al., 2011a; Peng et al., 2011; Tucker et al., 2011; Kong et al., 2012; Schallner et al., 2012; Szabadfi et al., 2012; Dorfman et al., 2013; Halder et al., 2013; Kiss et al., 2013; Salido et al., 2013a; Chrysostomou et al., 2014; Dreixler et al., 2014; Pan et al., 2014; Zhang et al., 2014; Halder et al., 2015; Ulbrich et al., 2015; Fan et al., 2016; Roth et al., 2016; Wang et al., 2016
Glutamate; NMDA	Fernandez et al., 2009a; Fernandez et al., 2009b; Dorfman et al., 2013; Salido et al., 2013a
Oxygen-Glucose Deprivation *(in vitro)*	Kwong et al., 2003; Brandt et al., 2011; Hamner et al., 2015
Phototoxicity	Barbe et al., 1988; Liu et al., 1998; Li et al., 2001; Grimm et al., 2002; Casson et al., 2003; Gao and Talalay, 2004; Tanito et al., 2005; Tanito et al., 2007; Ueki et al., 2008; Thiersch et al., 2009; Ueki et al., 2009; Lange et al., 2010; Natoli et al., 2010; Zhu et al., 2010; Albarracin et al., 2011; Lange et al., 2011; Ren et al., 2011; Albarracin and Valter, 2012; Bordone et al., 2012; Schatz et al., 2012; Lawson et al., 2014; Brandli et al., 2016; Chrenek et al., 2016; Kast et al., 2016
Oxidative Stress	Chollangi et al., 2009; Sharma et al., 2009; Yi et al., 2012
TNF-alpha	Li et al., 2011
Glaucoma	Park et al., 2001; Anderson et al., 2005; Belforte et al., 2011; Bosco et al., 2012; Howell et al., 2012; Zhu et al., 2012; Inman et al., 2013; Zhu et al., 2013; Johnson et al., 2014; Gidday et al., 2015b; Patel et al., 2015
Diabetic Retinopathy	Fernandez et al., 2011; Fernandez et al., 2012; Kim et al., 2013; Salido et al., 2013b; Dorfman et al., 2014
Retinal Degeneration	Lange et al., 2010; Hanif et al., 2015
ON Crush	Wang et al., 2010; Shibeeb et al., 2014; Chen et al., 2016
ON Transection	Liu et al., 2013; Liu et al., 2017

Table 2

Conditioning Stimuli

SYSTEMIC PHYSIOLOGIC STIMULI	
Brief Ischemia	Roth et al., 1998; Li and Roth, 1999; Lin and Roth, 1999; Li et al., 2000; Nishiyama et al., 2000; Ettaiche et al., 2001; Nonaka et al., 2001; Sakamoto et al., 2001; Zhang et al., 2002; Zhu et al., 2002; Casson et al., 2003; Li et al., 2003; Sakamoto et al., 2004; Wu et al., 2006; Zhu et al., 2006; Kamphuis et al., 2007a; Kamphuis et al., 2007b; Nishijima et al., 2007; Dreixler et al., 2008; Ding et al., 2009; Dreixler et al., 2009a; Dreixler et al., 2009b; Dreixler et al., 2009c; Fernandez et al., 2009a; Fernandez et al., 2009b; Husain et al., 2009; Dreixler et al., 2010; Stowell et al., 2010; Belforte et al., 2011; Dreixler et al., 2011c; Dreixler et al., 2011b; Dreixler et al., 2011a; Fernandez et al., 2011; Fernandez et al., 2012; Salido et al., 2013b; Fan et al., 2016; Liu et al., 2017
Cyclic Light	Liu et al., 1998; Li et al., 2001; Tanito et al., 2007; Chollangi et al., 2009; Ueki et al., 2009; Zhu et al., 2010; Chrenek et al., 2016; de la Barca et al., 2017
Red Light	Natoli et al., 2010; Albarracin et al., 2011; Albarracin and Valter, 2012
Hypoxia	Grimm et al., 2002; Zhu et al., 2002; Zhu et al., 2007; Berkowitz et al., 2008; Thiersch et al., 2008; Peng et al., 2009; Thiersch et al., 2009; Lange et al., 2010; Zhu et al., 2012; Zhu et al., 2013; Gidday et al., 2015b; Kast et al., 2016
Hyperoxia	Wang et al., 2010; Zhu et al., 2010
Inhaled Gases (argon, CO, hydrogen, hydrogen suflide)	Gao and Talalay, 2004; Biermann et al., 2010; Biermann et al., 2011; Schallner et al., 2012; Ulbrich et al., 2015; Chen et al., 2016; Wang et al., 2016
Hyperthermia, Hypothermia	Barbe et al., 1988; Park et al., 2001; Kwong et al., 2003; Tucker et al., 2011; Salido et al., 2013a
Gamma Radiation	Anderson et al., 2005; Bosco et al., 2012; Howell et al., 2012
Brief Unilateral Carotid Occlusion	Hamner et al., 2015
Exercise	Kim et al., 2013; Chrysostomou et al., 2014; Lawson et al., 2014; Hanif et al., 2015; Chrenek et al., 2016
Dietary Interventions	Natoli et al., 2010; Kong et al., 2012; Zarnowski et al., 2012; Inman et al., 2013; Patel et al., 2015
Enriched Environments	Dorfman et al., 2013; Kiss et al., 2013; Dorfman et al., 2014
Remote Conditioning	Brandli and Stone, 2014; Zhang et al., 2014; Brandli et al., 2016; Liu et al., 2017
LOCAL PHYSIOLOGIC STIMULI	
Transcorneal Electrical Stimulation	Schatz et al., 2012
Gamma Radiation	Howell et al., 2012
Hypothermia	Salido et al., 2013a
Intravitreal LPS	Franco et al., 2008; Bordone et al., 2012; Halder et al., 2013
Intravitreal Prothymosin-α	Halder et al., 2015
Red Light	Natoli et al., 2010
SYSTEMIC PHARMACOLOGIC STIMULI	
Diazoxide	Roth et al., 2006; Dreixler et al., 2008; Dreixler et al., 2009a
Sevoflurane	Szabadfi et al., 2012
Zinc	Park et al., 2001
HIF Stabilizers	Badr et al., 1999; Whitlock et al., 2005; Zhu, 2008; Peng et al., 2011; Ren et al., 2011
Erythropoietin	Grimm et al., 2002; Junk et al., 2002
Sulforaphane	Gao and Talalay, 2004; Tanito et al., 2005; Pan et al., 2014
LOCAL PHARMACOLOGIC STIMULI	
Diazoxide	Ettaiche et al., 2001

Leukemia Inhibitory Factor (LIF)	Ueki et al., 2008
NMDA	Ahn et al., 2008
Tunicamycin	Li et al., 2011
Mesenchymal Stem Cell-Conditioned Media	Dreixler et al., 2014; Roth et al., 2016

Table 3

Cross Tolerance

Injury Model	Conditioning Stimulus	
Retinal Ischemia	**Hypoxia**	Zhu et al., 2002; Zhu et al., 2007; Peng et al., 2009
	HIF Mimetics	Badr et al., 1999; Whitlock et al., 2005; Zhu, 2008; Peng et al., 2011
	K-ATP Agonists	Roth et al., 2006; Dreixler et al., 2008; Dreixler et al., 2009
	Carbon Monoxide	Biermann et al., 2010; Schallner et al., 2012
	Hydrogen Gas	Wang et al., 2016
	Argon	Ulbrich et al., 2015
	Hydrogen Sulfide	Biermann et al., 2011
	Sulforaphane	Pan et al., 2014
	Hyperthermia	Tucker et al., 2011
	Hypothermia	Salido et al., 2013a
	LPS and Toll-like Receptor Agonists	Franco et al., 2008; Halder et al., 2013; Halder et al., 2015
	Remote Conditioning	Zhang et al., 2014
	Environmental Enrichment	Dorfman et al., 2013; Kiss et al., 2013
	Dietary Interventions	Natoli et al., 2010; Kong et al., 2012; Zarnowski et al., 2012
	Exercise	Chrysostomou et al., 2014
Phototoxicity	**Brief ischemia**	Casson et al., 2003
	Hypoxia	Grimm et al., 2002; Thiersch et al., 2009; Lange et al., 2010
	Hyperoxia	Zhu et al., 2010
	Hyperthermia	Barbe et al., 1988
	Transcorneal Electrical Stimulation	Schatz et al., 2012
	HIF overexpression	Lange et al., 2011
	Erythropoietin	Grimm et al., 2002
	Sulforaphane	Tanito et al., 2005
	Pyruvate	Ren et al., 2011
	Leukemia Inhibitory Factor (LIF)	Ueki et al., 2008
	LPS	Bordone et al., 2012
	Remote Conditioning	Brandli et al., 2016
	Exercise	Lawson et al., 2014; Chrenek et al., 2016
Glaucoma	**Intermittent Hypoxia**	Zhu et al., 2012; Gidday et al., 2015b
	Intermittent Ischemia	Belforte et al., 2011
	Gamma Radiation	Anderson et al., 2005; Bosco et al., 2012; Howell et al., 2012; Johnson et al., 2014
	Zinc	Park et al., 2001
	Hyperthermia	Park et al., 2001
	Dietary Interventions	Inman et al., 2013; Patel et al., 2015

Injury Model	Conditioning Stimulus	
Diabetic Retinopathy	**Brief ischemia**	Fernandez et al., 2011; Fernandez et al., 2012; Salido et al., 2013b
	Exercise	Kim et al., 2013
	Environmental Enrichment	Dorfman et al., 2014
ON Crush or Transection	**Hyperoxia**	Wang et al., 2010
	Carbon Monoxide	Chen et al., 2016
	Remote Conditioning	Liu et al., 2013

TABLE 4

Post-Conditioning

Injury Model	Conditioning Stimulus	
Retinal Ischemia	**Brief Ischemia**	Fernandez et al., 2009a; Fernandez et al., 2009b; Dreixler et al., 2010; Dreixler et al., 2011a; Dreixler et al., 2011b
	Argon	Ulbrich et al., 2015
	Carbon Monoxide	Schallner et al., 2012
	Hydrogen Gas	Wang et al., 2016
	Stem Cell-Conditioned Media	Dreixler et al., 2014; Roth et al., 2016
	Remote Conditioning	Zhang et al., 2014
	Environmental Enrichment	Dorfman et al., 2013
Diabetic Retinopathy	**Intermittent Brief Ischemia**	Fernandez et al., 2011; Fernandez et al., 2012
	Environmental Enrichment	Dorfman et al., 2014
Phototoxicity	**Pyruvate**	Ren et al., 2011
	Red Light	Natoli et al., 2010; Albarracin and Valter, 2012
Glaucoma	**Intermittent Hypoxia**	Gidday et al., 2015b
	Intermittent Hyperthermia	Park et al., 2001
	Intermittent Zinc	Park et al., 2001
ON Crush	**Carbon Monoxide**	Chen et al., 2016

TABLE 5

Resilient Phenotypes

	Injury Model			
Phenotypes	**Ischemia**	**Phototoxicity**	**Glaucoma**	**Diabetes**
Anti-apoptotic	Zhang et al., 2002; Dreixler et al., 2008; Peng et al., 2009; Biermann et al., 2010; Biermann et al., 2011; Schallner et al., 2012; Ulbrich et al., 2015	Grimm et al., 2002; Bordone et al., 2012		Kim et al., 2013
Anti-inflammatory	Nishiyama et al., 2000; Nonaka et al., 2001; Fernandez et al., 2009a; Fernandez et al., 2009b; Biermann et al., 2010; Biermann et al., 2011; Schallner et al., 2012; Halder et al., 2013; Chrysostomou et al., 2014; Pan et al., 2014; Zhang et al., 2014; Wang et al., 2016	Zhu et al., 2010; Albarracin et al., 2011; Albarracin and Valter, 2012	Bosco et al., 2012; Howell et al., 2012	Fernandez et al., 2011; Fernandez et al., 2012; Salido et al., 2013; Dorfman et al., 2014
Anti-oxidative stress	Zhu et al., 2007; Peng et al., 2009; Peng et al., 2011; Kong et al., 2012; Pan et al., 2014; Zhang et al., 2014; Ulbrich et al., 2015; Wang et al., 2016		Inman et al., 2013	Salido et al., 2013b
Anti-lipid peroxidation		Zhu et al., 2010; Bordone et al., 2012	Belforte et al., 2011; Inman et al., 2013	
Changes in metabolism	Nishiyama et al., 2000; Berkowitz et al., 2008; Fernandez et al., 2009a; Biermann et al., 2011; Kong et al., 2012	Barbe et al., 1988	Park et al., 2001	Fernandez et al., 2012
Changes in signaling intermediates	Dreixler et al., 2009; Biermann et al., 2010; Biermann et al., 2011; Schallner et al., 2012; Ulbrich et al., 2015	Ueki et al., 2008		Kim et al., 2013
Increased mitogens		Lawson et al., 2014; Brandli et al., 2016		Dorfman et al., 2014
Improved tissue perfusion	Lin and Roth, 1999			
Improved vascular integrity				Fernandez et al., 2011; Salido et al., 2013b; Dorfman et al., 2014
Improved axonal transport		Bosco et al., 2012; Inman et al., 2013		Fernandez et al., 2012
Epigenetic modifications	Stowell et al., 2010; Fan et al., 2016			