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The Protective Role of GRP78 Against Blue Light Hazard

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Abstract

GRP78, a pivotal chaperone protein residing in the endoplasmic reticulum, effectively mitigates cellular damage inflicted by blue light. It exerts this protective function through multiple mechanisms, including the suppression of blue light-induced oxidative stress, facilitation of protein repair damaged by blue light, and inhibition of blue light-mediated apoptosis. GRP78's pivotal role in defending against blue light damage underscores its potential as a novel target for developing effective blue light protection strategies. Future endeavors delving into the mechanisms and functions of GRP78 may yield efficient drugs and preventive measures against blue light hazards, thereby safeguarding human health.

Keywords: blue light, GRP78, retinal pigment epithelium, lipofuscin, oxidative stress, cancer cells

1. Definition and Sources of Blue Light

Blue light (BL), also known as High Energy Visible Light (HEV), encompasses the blue component of the visible light spectrum, spanning 380-760 nm, with a particularly potent range between 400-500 nm. Short-wavelength blue light (400-455 nm) possesses high energy and readily penetrates the lens, reaching the retinal macula and potentially causing damage. Conversely, blue light within 480-500 nm regulates circadian rhythms, influencing sleep patterns, mood, and memory, thus conferring beneficial effects (Wang, L., et al., 2023).

Solar radiation constitutes the primary source of blue light, while electronic devices such as computer monitors, flat-screen TVs, smartphones, tablets, and fluorescent bulbs also emit blue light. Lifestyle shifts, including decreased outdoor activities and increased screen time from LEDs, fluorescent lamps, and electronic displays, have altered human blue light exposure patterns (Cao, M., Xu, T., & Yin, D, 2023).

The widespread adoption of Light-emitting Diodes (LEDs) has sparked concerns regarding their ocular hazards. Ultraviolet (UV) light below 300 nm and most UV within 300-400 nm is filtered by the cornea and lens, limiting retinal exposure to short-wavelength light primarily within 400-500 nm. The International Commission on Non-Ionizing Radiation Protection (ICNIRP) has set a threshold of 110 kJ/m^2 as the toxic dose of blue light from ocular devices, capable of inducing macroscopically

observable retinal pathologies (Cao, M., Xu, T., & Yin, D., 2023). Mounting evidence underscores the deleterious effects of chronic exposure to blue light (400-500 nm) on retinal oxidative stress and severe damage (Suitthimeathegorn, O., Yang, C., Ma, Y., & Liu, W, 2022).

2. Mechanisms of Blue Light-Induced Ocular Damage

Blue light (BL), characterized by its short wavelength and high energy, exerts irreversible photochemical damage to ocular tissues due to its relatively high energy content. Excessive exposure to blue light often triggers a cascade of ocular tissue alterations, encompassing oxidative stress, mitochondrial apoptosis, inflammatory apoptosis, intracellular apoptosis within mitochondria, and DNA damage (Ouyang, X., Yang, J., Hong, Z., Wu, Y., Xie, Y., & Wang, G, 2020).

Blue light-induced retinal pathology stems from photochemical rather than thermal injury (Ham, W. T., et al., 1978). The retina serves as the receptor for light signals, with photoreceptors (cones and rods) and retinal pigment epithelial cells (RPE) being pivotal in visual processing. RPE cells harbor two types of pigment granules: melanin located atop the cells and lipofuscin at their basal end. Lipofuscin is primarily composed of N-retinylidene-N-retinylethanolamine (A2E) and its oxidative products. Overexposure to blue light initiates mitochondrial damage, leading to aberrant generation of reactive oxygen species (ROS), photoreceptor loss, lipid peroxidation, and cell apoptosis. The synergistic effect of blue light and A2E, along with photo-bleaching and reverse photochemistry, further exacerbates photochemical damage, activating inflammatory responses, DNA damage, and suppression of mitochondrial and lysosomal functions.

2.1 Mitochondrial Damage

Mitochondria, as crucial organelles for reactive oxygen species (ROS) production, undergo excessive oxidative stress leading to ROS overgeneration and disrupted oxidative phosphorylation (Jeong, S. Y., Gu, X., & Jeong, K. W, 2019), thereby impairing their function and structure, ultimately triggering death signaling pathways involving mitochondria.

To further investigate mitochondrial alterations, ARPE-19 cells were cultured in vitro, and mouse eyeballs were exposed to 460 nm blue light for two weeks prior to enucleation and sectioning. Under transmission electron microscopy, mitochondrial morphology was assessed, revealing substantial disruption and vacuolization in RPE cells from blue light-treated mice. This exposure disrupted the mitochondrial structure, with membranes partially or completely disintegrating.

Mitochondrial dynamics are orchestrated by fusion and fission proteins. To elucidate the relationship between blue light damage and mitochondrial function, mitochondrial-related markers were analyzed at the protein level in extracted mouse retinal tissue. Excessive ROS stimulates mitochondrial fission by altering the expression of dynamics-related proteins, with upregulation of the fission protein Drp1 and downregulation of the fusion protein Mfn2 (Li, J. Y., et al., 2018).

Excessive blue light exposure leads to ROS overproduction in retinal tissue mitochondria, activating the NLRP3 inflammasome, which triggers innate immune responses by releasing proinflammatory cytokines, initiating inflammation (Kuse, Y., Tsuruma, K., Kanno, Y., Shimazawa, M., & Hara, H, 2017; Hu, Z., et al., 2016; Narimatsu, T., et al., 2015). Excess ROS also disrupts calcium homeostasis, causing calcium overload (Lu, B., et al., 2017). Elevated calcium levels alter mitochondrial membrane potential, further promoting ROS generation. Changes in membrane potential increase membrane permeability and outer membrane rupture, releasing apoptosis-inducing factor 1 and oxidative enzymes into the cytoplasm, triggering apoptosis (Grimm, C., et al., 2001; 2000). In summary, excessive blue light exposure leads to ROS overproduction, oxidative stress, mitochondrial structural and functional damage, inflammation, and ultimately RPE apoptosis.

2.2 Lipofuscin Accumulation

A2E, a major component of lipofuscin, is a blue light-absorbing retinal pigment with autofluorescence and phototoxicity (Brunk, U. T., & Terman, A, 2002). Excessive lipofuscin accumulation in RPE enhances its sensitivity to blue light. Exposure to 460 nm blue light stimulates A2E to generate substantial ROS (Lamb, L. E., & Simon, J. D., 2004; Otsu, W., et al., 2020), leading to RPE apoptosis and damage via peroxidation. A2E is a major risk factor for RPE apoptosis, residing in RPE phagolysosomes. During lysosomal phagocytosis, autophagy may

contribute to A2E accumulation. When A2E reaches critical concentrations, it inhibits lysosomal proton pump function, causing lysosomal contents to leak into the cytoplasm and damaging DNA and mitochondrial membranes, thereby inducing RPE apoptosis (Grimm, C., et al., 2001).

Upon light or specific wavelength blue light exposure, A2E undergoes photoisomerization, releasing free radicals that alter RPE membrane and lysosomal membrane structure and function, directly or indirectly affecting lysosomal enzyme activity, resulting in RPE apoptosis.

2.3 Rhodopsin-Mediated Photodamage

As the chromophore in rod cells, rhodopsin plays a vital role in retinal light reception and scotopic vision. Blue light's conversion of rhodopsin damages both cone and rod photoreceptors, causing visual blurring. Rhodopsin's presence significantly enhances retinal photon capture under blue light, increasing light-induced cell death (Leibovitch, I., et al., 2006).

2.4 Mechanism of Lens Damage

The lens contains substances capable of absorbing blue light, which, upon exposure, generate derivatives that accumulate within the lens, leading to yellowing and opacity, ultimately contributing to the development of cataracts (Feng, J., et al., 2014). Blue light can also induce the production of reactive oxygen species (ROS) in the mitochondria of human lens epithelial cells (HLECs), augmenting the release of proinflammatory cytokines and chemokines, triggering cell apoptosis and predisposing to ocular diseases such as dry eye and cataracts. Researchers illuminated mice with short-wavelength blue LED light in a 12-hour light/dark cycle and examined the expression levels of Caspase-1, Caspase-11, and Gasdermin D in HLECs, concurrently observing cataract formation. Notably, exposure to blue LED light significantly elevated the expression of Caspase-1, Caspase-11, and GSDMD in rats, accompanied by cataract development and a marked increase in the double-positive proportion of lens epithelial cells. These findings suggest that therapeutic strategies aimed at preventing HLEC apoptosis may inhibit the expression of relevant apoptotic factors, potentially benefiting the treatment of age-related cataracts.

3. GRP78 Concept and Its Role in Blue Light-Induced Protection

GRP78 (also known as 78-kDa glucose-regulated protein) serves as a pivotal endoplasmic reticulum (ER) chaperone protein, crucial for ER protein quality control and regulating the activation of ER transmembrane signaling molecules. Its primary function is to facilitate the folding of other cellular proteins. However, under specific pathological conditions, such as SARS-CoV-2 infection or tumor progression, GRP78's functionality undergoes alterations.

In the context of blue light-induced damage, GRP78 plays a significant role. Blue light can elicit oxidative stress and damage to cells, and GRP78, as a crucial molecular chaperone in the ER, exerts the following functions:

3.1 Maintaining ER Homeostasis

Upon blue light exposure, particularly in retinal pigment epithelial (RPE) cells containing vinyl-N-vinyl ethanolamine (A2E), there is an increase in two major ER stress molecules: GRP78 and C/EBP homologous protein (CHOP), indicating GRP78's involvement in the pathogenesis of oxidative damage in RPE cells induced by blue light (Nishitoh H, 2012; Li, J., et al., 2008). Recently, it has been implicated in stress-induced autophagy regulation (Yorimitsu, T., & Klionsky, D. J., 2007). Autophagy, a highly conserved "self-eating" mechanism in eukaryotic cells, degrades and recycles cytosolic components via lysosomal degradation pathways (Mehrpour, M., et al., 2010). The initiation of autophagy involves the formation of phagophores, which expand into double-membraned vesicles called autophagosomes that sequester cellular materials as cargo for subsequent fusion with lysosomes for degradation (Yorimitsu, T., & Klionsky, D. J., 2005). Various biochemical and pathological stresses can induce autophagy, whose proper activation clears harmful cellular components and damaged organelles, restoring intracellular homeostasis (Vilchez, D., Saez, I., & Dillin, A., 2014).

3.2 Modulating Cellular Stress Responses

Under oxidative stress, GRP78 dissociates from immunoglobulin heavy chain-binding protein (BiP), triggering BiP oligomerization and ultimately initiating the unfolded protein response (UPR) to aid in protein folding during ER stress (Hetz, C., Zhang, K., & Kaufman, R. J., 2020). The UPR, a cellular response to the accumulation of unfolded or misfolded proteins

in the ER, activates signaling pathways to maintain ER homeostasis and promote cell survival by enhancing ER protein-folding capacity, preventing the aggregation of unfolded proteins, and thereby safeguarding cells from deleterious effects (Wang, M., Wey, S., Zhang, Y., Ye, R., & Lee, A. S., 2009).

4. Limitations of GRP78 in Blue Light-Induced Damage Protection

When significant accumulation of intracellular lipofuscin occurs in retinal pigment epithelial (RPE) cells and these cells are exposed to blue light, A2E acts as a photosensitizer for the generation of singlet oxygen and superoxide radicals, triggering RPE cell damage (Pizzo, S. V., 2018). Oxidative stress, induced by reactive oxygen species (ROS), leads to cellular impairment. Cellular stress alters the ratio of reduced to oxidized molecular chaperones essential for proper protein folding. Under these conditions, misfolded and unfolded proteins accumulate in the endoplasmic reticulum (ER) lumen, eliciting ER stress. GRP78, an ER-resident protein, exerts protective effects in blue light-mediated RPE cell injury by activating the unfolded protein response (UPR), which facilitates refolding of misfolded proteins and subsequently activates cellular protein clearance mechanisms. However, subsequent downregulation of GRP78 expression is associated with reduced cell viability (Gopal, U., & Pizzo, S. V., 2018; Tsai, Y. L., & Lee, A. S., 2018).

4.1 Implications of Elevated GRP78 Expression in Cancer Cells

Overexpression of GRP78 enables a fraction of the protein to escape sequestration and translocate to the cell surface, where it interacts with various ligands and other proteins, functioning as a multifunctional receptor. CS-GRP78 (cell surface GRP78) plays pivotal roles in cell signaling, proliferation, migration, invasion, apoptosis, inflammation, and immunity (Tsai, Y. L., & Lee, A. S., 2018).

In conditions such as hypoxia, glucose starvation, or tumorigenesis, CS-GRP78 levels can increase substantially, with hypoxia leading to a fourfold or greater increase. Elevated CS-GRP78 levels correlate with various pathological conditions, including multiple cancers, osteoarthritis, and rheumatoid arthritis. The presence of CS-GRP78 on the cell surface elicits autoimmune responses from the immune system and promotes the production of circulating autoantibodies against CS-GRP78-expressing cells (Al-Hashimi, A. A., Rak, J., & Austin, R. C., 2018; Gopal, U., & Pizzo, S. V., 2021; Dudek, J., Benedix, J. & Cappel, S., 2009).

As a stress-inducible, multifunctional, pro-survival ER chaperone belonging to the heat shock protein 70 (Hsp70) family, CS-GRP78 is implicated in enhanced malignant behavior and resistance to chemotherapy and radiotherapy in various cancer cells by promoting proliferation, altering metabolism, improving survival, and enhancing invasive and metastatic potential. Emerging evidence suggests that CS-GRP78 exerts an unusual role in regulatory transcription factors (TFs), mediating signaling pathways involved in malignant transformation, metabolic reprogramming, and tumor progression (Gopal, U., & Pizzo, S. V., 2021). Notably, GRP78 is closely associated with lung cancer progression and poor prognosis, highlighting its significance in lung cancer treatment.

4.2 Disease Risks Associated with Artificially Manipulating GRP78 Expression

GRP78, a member of the Hsp70 family, relies heavily on numerous interacting partners, including co-chaperones, nucleotide exchange factors, and signaling molecules. Various diseases are linked to GRP78 and its interaction partners, including infectious diseases caused by Shiga toxin-producing Escherichia coli. Additionally, genetic disorders such as Marinesco-Sjögren syndrome, autosomal dominant polycystic liver disease, Wolcott-Rallison syndrome, and several cancer types can be considered BiP-related diseases (Dudek, J., Benedix, J. & Cappel, S., 2009).

4.3 Adverse Effects of Artificially Manipulating GRP78 Expression on PERK and IRE1

PERK and IRE1 are type I transmembrane protein kinases residing in the ER that transmit stress signals upon protein-folding perturbations. The luminal domains of these proteins are functionally interchangeable in mediating the ER stress response. In unstressed cells, both luminal domains form stable complexes with the ER chaperone BiP. Protein-folding perturbations promote reversible dissociation of BiP from the luminal domains of PERK and IRE1. Loss of BiP correlates with the formation of

high-molecular-weight complexes that activate PERK or IRE1, while BiP overexpression attenuates their activation (Dudek, J., Benedix, J. & Cappel, S., 2009; Bertolotti, A., Zhang, Y. & Hendershot, L., 2000). These findings align with a model in which BiP inhibits signaling through PERK and IRE1, and protein misfolding alleviates this inhibition by affecting the release of BiP from the luminal domains of PERK and IRE1.

5. Suggestions, Prospects, and Improvement Measures

5.1 Modulation of GRP78 Overexpression

To reduce the expression of over-expressed GRP78 on cancer cell surfaces, thereby mitigating cancer cell proliferation and invasion, the development of specific inhibitors is crucial. Employing high-throughput screening and computer-aided drug design (CADD) can facilitate the discovery of small-molecule inhibitors that specifically bind to GRP78 and disrupt its function. Additionally, investigating the regulatory mechanisms of the KDEL receptor under various pathological conditions is an essential avenue. Developing molecules that enhance KDEL retention may prevent GRP78 from escaping the endoplasmic reticulum (ER) to the cell surface, subsequently reducing its expression on cancer cells.

5.2 Combination Therapy Strategies

Given the potential for GRP78-targeted therapy to induce cancer cell resistance, combination treatments with other anticancer agents are imperative. Such combinations, including chemotherapy, radiotherapy, or drugs targeting other molecular chaperones or ER stress responses, have shown to significantly enhance therapeutic efficacy. This multi-target approach heightens cancer cell sensitivity and reduces resistance.

5.3 Cell-Specific Regulation of GRP78 Function

Researching the functional differences of GRP78 across cell types and developing strategies to specifically modulate its activity in normal versus cancer cells is pivotal. Leveraging gene editing technologies like CRISPR/Cas9 can precisely regulate GRP78 expression, minimizing side effects in cancer treatment. Furthermore, developing gene therapies specifically targeting cancer cells through targeted delivery systems enhances treatment specificity and effectiveness.

6. Future Research Directions

6.1 Deepening Insights into GRP78 Functions Across Pathological States

Future endeavors should delve deeper into GRP78's roles in non-cancerous diseases like atherosclerosis and rheumatoid arthritis. These investigations can unravel GRP78's functionalities under various pathological conditions, paving the way for broader therapeutic strategies. In neurodegenerative disorders like Alzheimer's and Parkinson's, elucidating GRP78's protective mechanisms in neurons could inspire novel therapeutic targets to slow or halt disease progression.

6.2 Exploring GRP78's Role in the Immune System

While GRP78's functions in immune cells remain elusive, its potential significance in autoimmune diseases warrants attention. Studying GRP78's specific roles and regulatory mechanisms in immune cells could offer new therapeutic targets for autoimmune disorders. Insights into GRP78's modulation in inflammatory responses could inform anti-inflammatory strategies.

6.3 Protective Applications Against Blue Light-Induced Damage

For antioxidant applications, developing more potent antioxidants or combination therapies, while examining their metabolism and safety in humans, is crucial. Nanotechnology could enhance efficacy by directly delivering antioxidants to damaged ocular tissues. Mitochondrial protectants require further exploration of mitochondrial dynamics, aiming to create novel drugs that safeguard mitochondrial function, considering long-term safety and efficacy. Regarding A2E accumulation, clarifying its metabolism and elimination mechanisms could yield drugs or treatments to accelerate A2E clearance. Gene editing could regulate relevant gene expression, diminishing A2E build-up. Screening natural or synthetic compounds for rhodopsin protection and validating their effects through clinical trials is also necessary. Similarly, protective agents for lens epithelial cells could be identified through high-throughput screening, progressing to animal and human trials.

7. Conclusion

Blue light, a high-energy visible light present in sunlight, electronic screens, and LED lights, penetrates the cornea and lens to reach the retina, damaging retinal pigment epithelial cells

and accelerating macular degeneration. GRP78, a vital ER molecular chaperone, safeguards ER homeostasis and cell survival. Its activation of cellular defense mechanisms mitigates blue light-induced ocular damage, including antioxidant stress and apoptosis inhibition. However, GRP78's protective role against blue light is limited, necessitating further exploration via genetic engineering to boost GRP78 expression, novel GRP78 agonists, and combined ocular protection strategies for more effective blue light damage resistance.

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