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Nanoceria as Promising Ophthalmic Therapeutics for Retinal Diseases

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Many retinal diseases including prematurity, inherited retinal degeneration, diabetic retinopathy, retinitis pigmentosa, glaucoma and age-related macular degeneration (AMD) are the leading causes of blindness among infants, adults and elders in the world [1]. The retina of our eye is highly susceptible to oxidative stress due to its large oxygen consumption and high metabolic activity associated with exposure to light. This imbalance between the production of reactive oxygen species (ROS) and detoxification by antioxidant defense system results in excessive ROS levels, leading to damage of lipids, proteins and nucleic acids in retina cells.

Nanotechnology offers exciting new approaches for biology and medicine. In recent years, rare earth metal nanoparticles especially cerium oxide nanoparticles or nanoceria are showing potential as antioxidants in a wide range of biomedical applications [2]. The underlying molecular mechanism for the antioxidant action is their dual oxidation state depending on the reaction conditions. Nanoceria can switch between Ce^{4+} and Ce^{3+} creating an oxygen vacancy and thereby mimic biological antioxidants such as superoxide dismutase and catalase for protecting cells from oxidative stress [1,2]. Moreover, due to its oxygen buffering capacity, CNPs can self-regenerate to the initial Ce^{3+} state without entering into any deleterious side reactions during regeneration [2]. Thus, nanoceria has the capability to act as free radical scavenger reducing the ROS levels and possesses various biological applications including neuroprotective, radioprotective, cardioprotective, anti-inflammatory, anti-invasive, pro-oxidative and antioxidative, anti-angiogenic, pro-apoptotic and anti-apoptotic properties [2,3]. In recent years, much attention has been drawn on the potential use of nanoceria as therapeutic antioxidants for treatment of oxidative stress related diseases especially retinal diseases [4-9].

Nanoceria (20 μL of 1 mM) has been shown to protect the retina of tubby mice with retinal degeneration by decreasing ROS, upregulating the expression of neuroprotection-associated genes, downregulating apoptosis signaling pathways and upregulating survival signaling pathways to slow down photoreceptor degeneration [4]. In another study, a very small amount (172 ng) of nanoceria was demonstrated to prolong photoreceptor survival and preserve retinal structure and function in tubby mutant mice for more than a month following a single intravitreal injection [5]. More interestingly, nanoceria could inhibit various major pro-inflammatory cytokines and pro-angiogenic growth factors including tslp, Lif, Il3, Vegfa, Fgft, Fgf7, Egf, Efna3, Lep and up-regulation of several cytokines and anti-angiogenic genes in retinas of Vldlr-/- mice within one week following single intravitreal injection, suggesting a great potential of nanoceria to treat AMD, retinal angiomatous proliferation and other neurodegenerative diseases [6]. To add further evidence, nanoceria has been shown to reduce microglial activation and their migration to outer nuclear layer in retina of albino Sprague-Dawley rats exposed to light

at 1000 lux for 24h [7]. Answering to the questions of nanoceria's toxicity in retina, no acute or long-term negative effects of nanoceria on retinal function and cytoarchitecture was observed even after retaining in retina for 120 days [8]. In addition, nanoceria did not cause any damage to retina 30 days after intravitreal injection into wild-type C57BL/6J mice at doses ranging from 17.2 to 1720 ng per eye as no cellular infiltration or elevation in inflammatory responses was observed [9].

All in all, nanoceria being safe and effective at low dosages can be a potential ophthalmic therapeutic for the treatment of retinal diseases. However, a more detailed mechanistic studies are necessary before nanoceria's application could be extended to human subjects in clinical studies.

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