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Keeping the lights on: a new role for an old drug to support cone survival in Retinitis Pigmentosa

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A B S T R A C T

Retinitis Pigmentosa (RP) is an incurable disorder characterized by progressive vision loss due to photoreceptor degeneration, typically following a rod-cone sequence. Rods die first, driven by primary genetic mutations; cones then degenerate secondarily through bystander mechanisms. As cones mediate daylight and high-acuity vision, crucial to human visual function, even partial preservation of these cells can profoundly enhance quality of life, regardless of the underlying genetic defect. Although significant progress has been made in understanding RP genetics and developing targeted therapies such as gene augmentation, a universal cure remains out of reach. This review centers on the biological drivers of secondary cone degeneration, with a focus on oxidative stress, metabolic dysfunction, and inflammation. Inflammation, now recognized as a key contributor to RP progression, involves the activation of microglia and infiltration by macrophages, both of which exacerbate retinal damage and offer promising therapeutic targets. We briefly survey current treatment modalities that have advanced to clinical application, including gene therapies, retinal prostheses, and neuroprotective strategies. Building on this therapeutic landscape, we propose a rationale for exploring ocular glucocorticoids—specifically dexamethasone—as a treatment avenue. Recent in vivo evidence from the rd10 mouse model demonstrates that intraocular dexamethasone, a long-approved agent for ocular inflammation, can preserve cone photoreceptors and protect the retinal pigment epithelium, a critical barrier for retinal homeostasis.

Glucocorticoids may thus represent a class of mutation-agnostic therapeutics with strong translational promise. Their repurposing for RP could help safeguard photoreceptors and visual function, addressing a pressing and unmet clinical need.

1. Inherited retinal degenerations (IRDs): an overview

Inherited retinal degenerations comprise a genetically and clinically heterogeneous group of disorders characterized by progressive dysfunction and death of retinal cells, primarily photoreceptors and the retinal pigment epithelium (RPE). Collectively, IRDs affect roughly 1 in 3000–4000 individuals and are a leading cause of inherited blindness worldwide (Georgiou et al., 2021; Griffith et al., 2022).

The genetic basis of IRDs reveals a large variety, not commonly found in other genetic diseases, with over approximately 300 causative genes identified to date (Britten-Jones et al., 2023; Schneider et al., 2022). They encode, among others, proteins essential for phototransduction, outer segment structure, enzymes of the visual cycle, proteins involved in RPE function, retinal development, and synaptic physiology. Some genes code for transcription factors or splicing factors. Modes of inheritance are also diverse, comprising the Autosomal Recessive (AR, in 50–60 % of cases), Autosomal Dominant (AD, in 30–40 % of cases), X-linked (XL, in 5–15 % of cases) and the rare mitochondrial modalities, the latter often associated with systemic syndromes (https://www.fightingblindness.org/).

Several of the genes whose mutations are responsible for various forms of IRDs are critically involved in the structure and function of rod photoreceptors. For example, *PRPH2* encodes peripherin-2, a membrane-associated protein essential for the formation and stabilization of photoreceptor outer segment discs that house light-sensitive pigments. Another gene, *USH2A*, encodes for Usherin, a transmembrane protein vital for photoreceptor survival and is implicated in Usher syndrome, in which affected individuals show both RP and deafness. Additionally, some mutated genes are involved in intracellular transport, such as *ABCA4, which* encodes a large glycoprotein responsible for retinoid transport. Mutations in *ABCA4* are the primary cause of Stargardt disease, the most common form of inherited macular degeneration in young individuals. These few examples provide an idea of the wide range of functions carried by genes involved in IRDs, which,

Abbreviations: Retinitis Pigmentosa, (RP); Intravitreal Dexamethasone, (Dexa); Glucocorticoids, (GCs); Retinal Pigment Epithelium, (RPE); Outer Segments, (OS); Outer Nuclear Layer, (ONL); Inner Nuclear Layer, (INL).

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collectively, constitute one of the most genetically heterogeneous groups of Mendelian disorders identified to date (Hamel, 2006). Their remarkable locus and allelic heterogeneity are especially notable given the phenotypic specificity of these conditions to retinal organization and physiology. While comparable levels of genetic heterogeneity are observed in certain other disease categories, such as neurodevelopmental disorders (e.g., intellectual disability, autism spectrum disorder) and forms of skeletal dysplasia, these typically encompass broader phenotypic spectrums and syndromic presentations involving multiple organ systems. In contrast, the genetic complexity of IRDs is particularly striking for a group of disorders confined to a single sensory organ, highlighting their unique position among monogenic diseases.

2. Retinitis Pigmentosa

Retinitis Pigmentosa (RP), the most prevalent form of inherited retinal dystrophy (IRD), affects approximately 1 in 3500 to 1 in 4500 individuals worldwide, corresponding to an estimated 1.5 million affected people globally (Hanany et al., 2024).

More than 100 genes are associated with RP alone, with mutations that can be inherited in an autosomal dominant (32 genes, accounting for 30 % of all the cases), autosomal recessive (90 genes, with 50 % of the cases) or X-linked manner (4 genes only) (https://retnet.org/summaries#b-diseases); they can also occur as sporadic/simplex traits. Rare forms comprise X-linked dominant, mitochondrial, and digenic cases. RP can also occur as syndromic forms, specifically Usher syndrome (associated with deafness, as mentioned above) and Bardet-Biedl syndrome, in which vision loss is accompanied by obesity, polydactyly, intellectual disability, and other abnormalities. As for IRDs, the causative genes of RP are highly heterogeneous, with typical forms caused by mutations in phototransduction enzymes (e.g., RHO, RPGR, PDE, etc.) (Hamel, 2006; Hartong et al., 2006; Patel et al., 2016; Sorrentino et al., 2016; Rodríguez-Muñoz et al., 2020).

RP is typically characterized by primary degeneration of rod photoreceptors, secondary cone loss, and accumulation of RPE deposits (bone spicules) in the neural retina. Typical signs are also retinal blood vessel attenuation and optic disc waxy pallor. The manifestation of the disease is typically in late adolescence, with different speeds, and the phenotype worsens relentlessly until all useful sight is lost. Genetic heterogeneity and possible low levels of gene expression make it difficult to achieve molecular diagnosis for some mutations, which remain unidentified. The primary (and often gradual) death of rods, abundant in the periphery of the retina, leads to a restriction of the visual field known as “tunnel vision”. Although rod loss leads to noticeable symptoms, as decreased light sensitivity and night blindness, patients may initially adapt to these changes, particularly in well-lit environments, as humans are adapted to live in daylight conditions and use artificial illumination. Some patients may not recognize the extent of scotopic and peripheral vision loss until the disease has advanced significantly, leading to delayed diagnosis. In contrast, patients’ vision becomes seriously affected when, as the disease progresses, cones also die, causing a decline in visual acuity, contrast sensitivity, and color discrimination. As the disease progresses, the fovea eventually becomes affected, leading to central vision loss and a substantial decline in independent daily functioning. Mobility and navigation without assistance also become increasingly difficult (Thenappan et al., 2023). Although RP often advances slowly, with significant vision loss taking years to manifest, the continuous deterioration of visual function is frequently accompanied by feelings of social isolation, depression, and a diminished overall quality of life. A disease causing severe visual impairment, RP may be associated with increased mortality risk—both directly and indirectly—according to studies from Korea and by the Blue Mountains Eye Study, similar to findings for glaucoma and age-related macular degeneration (Cugati, 2007; Karpa, 2009; Na et al., 2017). This association is likely driven by the disease’s impact on quality of life, as well as the critical role that vision plays in overall human physiology and daily functioning. Inescapable vision loss, social isolation, risks associated with walking impairment, and comorbidity with other diseases might all contribute to decreased life expectancy. It is important to emphasize that these risk factors are influenced not only by the primary genetic defect underlying RP, but also by the indirect and detrimental consequences of the loss of vision, our dominant sensory modality and a key determinant of human physiology. The impact of RP on overall well-being highlights the critical need for therapeutic strategies aimed at preserving even a fraction of foveal cone photoreceptors, thereby delaying the loss of central visual function (Becherucci et al., 2023; Confalonieri et al., 2024; Nguyen et al., 2023; Thenappan et al., 2023).

3. The intriguing process of bystander death of cones

The secondary degeneration of cone photoreceptors in RP represents a puzzling phenomenon, as these cells do not harbor the primary causative mutations. The transmission of cell death from degenerating rods to otherwise healthy cones has been termed the bystander effect (Ripps, 2002) and has emerged as a compelling subject in contemporary biology and ophthalmology; yet its underlying molecular mechanisms remain incompletely elucidated (Fig. 1).

In life sciences, the “bystander effect” is defined as the biological response of a cell resulting from an event in an adjacent or nearby cell. Such effect depends on intercellular communication and often amplifies the consequences of the original event” (Mitchel, 2004; Najafi et al., 2014).

Initially described in the context of radiation biology, the term denotes deleterious effects observed in non-irradiated cells adjacent to irradiated counterparts and applies to several contexts (Azzam et al., 2003; Nagasawa and Little, 1992). Analogous processes are, in fact, well documented in virology, where immune responses or paracrine signaling from virus-infected cells can indirectly affect neighboring, uninfected cells. Similarly, in inflammatory cascades, an overabundance of proinflammatory cytokines may damage surrounding, initially unaffected tissues. In oncology, this concept has been extended to therapeutic interventions such as suicide gene therapy, where non-targeted cells may suffer collateral effects from treatments aimed at malignant neighbors (Dilber and Smith, 1997).

Despite its seemingly adverse nature, the bystander effect may possess evolutionary or adaptive significance, particularly in the preservation of tissue homeostasis, orchestration of immune defense, and containment of cellular damage. When a cell is compromised (whether by genetic mutations or viral infiltration), adjacent cells may undergo apoptosis or senescence to curtail the propagation of deleterious agents. For instance, during herpes simplex infections, uninfected surrounding cells may undergo apoptosis or enter a senescent state in response to inflammatory or stress signals, thereby preventing further viral propagation (Bosnjak et al., 2005). This process is conceptually akin to firebreaks in forest management, where selected, unburnt trees are sacrificed to arrest the spread of wildfire (Fig. 2).

Experimental data, both in vitro and in vivo, have suggested that the bystander effect may be mediated through direct cell-to-cell communication occurring via gap junctions. Ripps was the first to extrapolate this framework to photoreceptor degeneration, hypothesizing that toxic metabolites might transfer from dying rods to cones through these junctional conduits (Ripps, 2002). This notion was subsequently tested in two murine models of RP (Rhoˆ−/− and rd1), wherein Connexin 36 (Cx36) (the gap junction protein predominantly expressed by cones) was genetically ablated to disrupt rod-cone coupling. Interestingly, the temporal progression of cone degeneration remained unaltered in these double mutants compared to controls, thereby challenging the role of gap junctions in mediating this specific form of bystander cell death.

More recently, this conclusion has been contested through the application of an innovative neural network chip (NN-Chip), engineered to position individual neurons within ordered microwells interconnected by microchannels to favor synapse formation. Using this

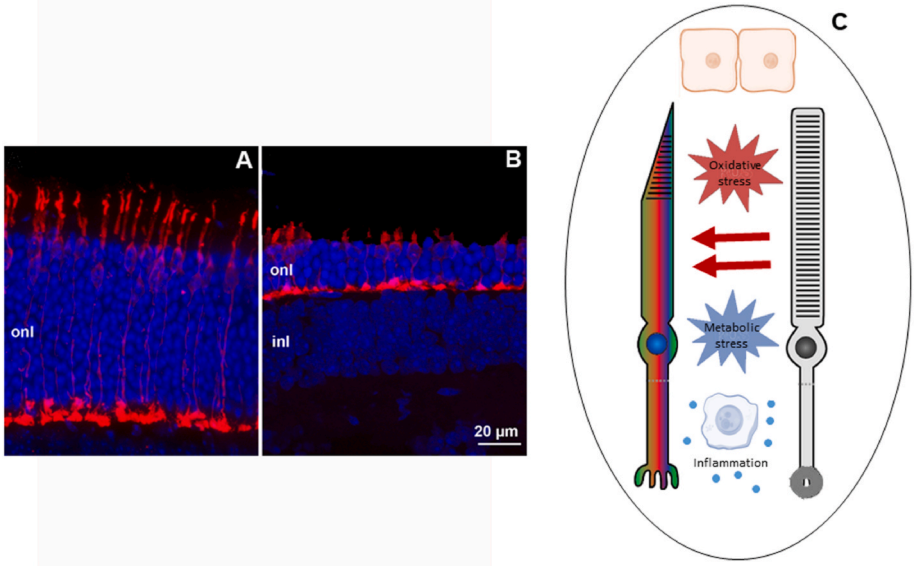

Fig. 1. A, B Elongated cones, stained red with cone arrestin antibodies, intermingle with rods in the wild type retina (A). Nuclei, stained blue by Hoechst, form a thick array in the outer nuclear layer (ONL). Cones are approximately 3 % of all the photoreceptors in the mouse. In the retina of rd10 mice aged 40 days (**B**), few rows of photoreceptors persist in the onl and surviving cones are shortened and remodeled. The death of rods creates biological responses which affect nearby cones (**C**).

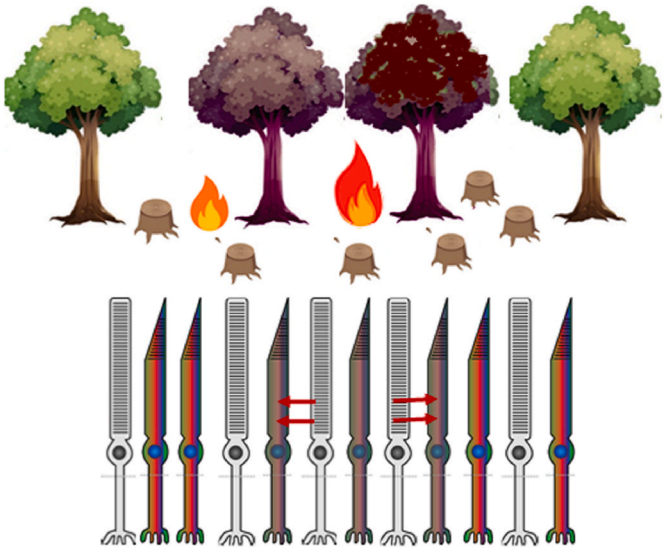

Fig. 2. The bystander death of cones arises as a consequence of non-cell-autonomous biological effects. The process might have an adaptive value, similar to the intentional burning of trees at the edge of a fire, to limit the spread of flames.

system, 661W cells, an immortalized line that mimics cones, were selectively overexposed to blue light within a confined region. Apoptotic signals were observed to disseminate from the irradiated zone to adjacent cells via gap junctions, a phenomenon significantly attenuated by their pharmacological blockade (Ma et al., 2018). However, despite its technological sophistication, this model does not fully replicate the complex cellular environment of the live retina, where the underlying biological mechanisms are considerably more intricate. Moreover, 661W cells represent immature photoreceptors and may exhibit a different gap junction architecture, potentially enhancing intercellular communication.

While the precise mechanisms underpinning secondary cone death in RP remain incompletely characterized, several converging factors, which include diminished levels of rod-derived cone viability factor (RdCVF), heightened oxidative stress, and chronic retinal inflammation, have consistently been implicated. These pathophysiological features are also relevant to age-related macular degeneration (AMD), a multifactorial condition in which therapeutic strategies aimed at broadly acting pathogenic mechanisms with pleiotropic potential offer the greatest promise (Murakami et al., 2020).

The schematic drawing on the right shows the main biological processes acting in the outer retina during the time shown in panel B: activation of microglia, transition from ramified to amoeboid shape, migration toward the outer retina, metabolic and oxidative stress. Alterations of the RPE, with breakdown of the outer retinal brain barrier also occur, altogether favoring cone death.

4. Photoreceptor death: a matter of STRESS

Photoreceptor survival is compromised when RP-causing mutations disrupt key cellular processes such as phototransduction, metabolism and intracellular transport. In turn, the disease creates a pathological environment that fosters adverse conditions contributing to its progression, in a sort of vicious circle. The following is a brief overview of stressors developing within the RP microenvironment that negatively affect the survival of both rods and cones. These include metabolic stress, oxidative stress, and inflammation.

4.1. *Metabolic stress*

The retina is among the most metabolically demanding tissues in the body, with photoreceptors accounting for most of its energy consumption. This high demand primarily supports phototransduction and the continuous renewal of outer segments. Photoreceptors remain depolarized in the dark and hyperpolarize in response to light. In darkness, maintaining the “dark current” requires significant ATP expenditure, primarily through the activity of Na^+/K^+-ATPase pumps (Narayan et al., 2017). Cones, being less sensitive to light than rods, are more frequently depolarized and consequently more vulnerable to metabolic stress (Country, 2017; Pan et al., 2021). Despite abundant oxygen availability

and the high efficiency of oxidative phosphorylation (OXPHOS), the mammalian retina relies heavily on aerobic glycolysis-a phenomenon known as the Warburg Effect (Vander Heiden et al., 2009; Pan et al., 2021). In photoreceptors of living organisms, glucose is the primary energy substrate, with 80–90 % of the glucose delivered to the outer retina being converted to lactate through aerobic glycolysis (Narayan et al., 2017; Pan et al., 2021).

Lactate is subsequently taken up by the retinal pigment epithelium (RPE), which expresses two isoforms of monocarboxylate transporters (MCTs) on its apical (MCT1) and basal membranes (MTC3) (Philp et al., 1998), and is utilized as an energy substrate (Kanow et al., 2017; Nolan et al., 2022; Hass et al., 2025; Chandler et al., 2025). The RPE also expresses low levels of hexokinase (HK), a rate-limiting enzyme in glycolysis, and its glucose metabolism is further inhibited by extracellular lactate, favouring the passage of non-metabolized glucose to photoreceptors (Hurley et al., 2015; Swarup et al., 2019; Hurley, 2021; De Jesus et al., 2022).

The role of Müller cells, which also express MCTs (Calbiague García et al., 2023), may differ between the outer and inner retina. In the outer retina, Müller cell processes adjacent to photoreceptors take up lactate generated through the glycolytic metabolism of these cells, in a manner analogous to the RPE (Lindsay et al., 2014; Hurley, 2021). In contrast, additional evidence suggests that Müller cells in the inner retina can supply lactate to meet the metabolic demands of retinal ganglion cells (Poitry-Yamate et al., 1995; Vohra and Kolko, 2020; Magistretti and Allaman, 2022).

Although aerobic glycolysis yields less ATP than OXPHOS, it provides several key advantages (Papaneophytou, 2024): it allows for rapid ATP generation and produces metabolic intermediates essential for biosynthetic pathways. These include substrates for glycan synthesis, the pentose phosphate pathway (PPP), and serine biosynthesis, critical for various cellular functions, including rhodopsin production (Murray et al., 2015). In addition, the PPP supports anabolic metabolism and generates NADPH, which protects cells from oxidative stress (Stincone et al., 2015). In turn, serine metabolism contributes to the synthesis of NADH/NADPH, sphingolipids, glutathione (GSH), and glycine. Furthermore, it has been demonstrated that the Warburg effect is necessary to maintain NAD+/NADH ratio when mitochondrial transporters exceed their ability to oxidize cytosolic NADH (Y. Wang et al., 2022). Thus, aerobic glycolysis supports not only energy production but also redox homeostasis and anabolic processes, essential for outer segment maintenance and function (Ng et al., 2015; Léveillard and Sahel, 2017).

Although photoreceptors rely on aerobic glycolysis, their high mitochondrial density suggests that OXPHOS may play a larger role than previously thought. A recent study (Y. Chen et al., 2024) argues that OXPHOS has been underestimated, partly because prior metabolic studies excluded the retinal pigment epithelium (RPE), biasing results toward glycolysis. Using intact retinal explants and NMR-based metabolomics, the study shows that rods, in particular, rely heavily on OXPHOS and engage in non-canonical pathways—such as the Cori, Cahill, and mini-Krebs cycles—which uncouple glycolysis from the full Krebs cycle, enabling rapid, localized ATP production suited to the retina's compartmentalized demands. The mini-Krebs cycle notably converts oxaloacetate to aspartate and then to N-acetylaspartate (NAA), offering an energy-efficient bypass of early Krebs steps. This may explain the high mitochondrial content despite glycolytic signatures. However, the regulation of these shunts remains unclear, and cell-type specificity is limited due to bulk tissue analysis. Single-cell studies are needed to refine our understanding.

Metabolically, the outer retina depends on a tight interplay with the RPE, which supplies oxygen and nutrients. In turn, photoreceptors export lactate, used by the RPE and Müller glia. This metabolic coupling is disrupted in retinal degeneration—or may itself contribute to disease. Rod loss alters glucose uptake, dampens mTOR signaling, and shortens cone outer segments (Iker Etchegaray et al., 2023; Lee et al., 2023; Sinha et al., 2020).

Cone degeneration is believed to be driven, at least in part, by nutrient deprivation (particularly glucose deficiency) as evidenced by changes in the expression of metabolic genes in RP. Restoring glucose availability has been shown to rescue cone structure and function, and subretinal injections of glucose restore outer segment synthesis in cones. Similarly, administration of rod-derived cone viability factor (RdCVF) enhances glucose uptake by stabilizing the glucose transporter GLUT1 in its active tetrameric form (Aït-Ali et al., 2015; Sahel and Léveillard, 2018; Xue and Cepko, 2024), enhancing cone viability.

Experimental approaches in RP models that have succeeded in increasing glucose availability at the retinal level have achieved a sizeable rescue of cones, otherwise destined to "starvation". Hence, targeting glucose metabolism, central to cone cell biology, might be a good strategy for rescuing these cells from bystander degeneration (Ayten et al., 2024; Caruso et al., 2025; Chertov et al., 2011; Daniele et al., 2022; Nolan et al., 2023; Petit et al., 2018).

4.2. *Oxidative stress*

RP is typically characterized by an initial phase of extensive rod photoreceptor degeneration. Rods are the most numerous cells in the retina and among the most metabolically active, with a high rate of oxygen consumption. The progressive death of rods significantly reduces oxygen consumption in the outer retina. However, the choroidal vasculature, which supplies this region, lacks intrinsic autoregulatory mechanisms and continues to convey high levels of oxygen irrespective of the reduced metabolic demand. The mismatch between oxygen supply and consumption leads to a pathological increase in tissue oxygen tension (pO_2), in particular in the outer retina, where cone photoreceptors reside.

Cones, metabolically demanding but not adapted to a hyperoxic environment, become exposed to chronic oxidative stress. The elevated oxygen availability promotes the generation of reactive oxygen species (ROS), including superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH) (Sies and Jones, 2020). This oxidative burden overwhelms the retinal antioxidant defense systems, which rely on enzymatic scavengers such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (Halliwell, 2006, 2007). As a result, oxidative damage accumulates within cone cells, affecting critical cellular structures and function. Mitochondria, both a source and target of ROS, become dysfunctional, impairing oxidative phosphorylation and leading to ATP depletion. Glycolytic flux is disrupted, and the failure of ATP-dependent ion pumps compromises membrane homeostasis, ultimately resulting in cone cell death (J. Wang et al., 2022).

Beyond intrinsic oxidative damage, ROS also act as signaling molecules that exacerbate neuroinflammation. Oxidative stress activates the local microglia and induces the recruitment of peripheral immune cells into the retina, amplifying local inflammatory responses. Pro-inflammatory cytokines and oxidative mediators released by activated microglia contribute to secondary injury, placing further stress not only on cones but also on surviving rods, overall accelerating photoreceptor degeneration (Khelfi, 2024).

Pioneering studies in rodent models of RP have substantiated the central role of oxidative stress in the pathophysiology of photoreceptor loss (Natoli et al., 2008). These investigations documented significant increases in retinal ROS levels and corresponding markers of oxidative damage during degeneration. Pharmacological or genetic interventions targeting oxidative stress demonstrated protective effects on surviving photoreceptors, stimulating a wave of preclinical studies eventually leading to clinical trials focused on antioxidant therapy (Haruta et al., 2009).

One such compound, N-acetylcysteine (NAC), a well-established mucolytic agent and antidote for acetaminophen toxicity, has attracted attention for its potent antioxidant properties. NAC exerts direct ROS-scavenging activity and serves as a precursor to cysteine, a rate-

limiting substrate in the synthesis of glutathione, a major intracellular antioxidant (Lee et al., 2011). A clinical study completed in 2022 evaluated the safety and functional effects of oral NAC administration in RP patients over a 24-week period. Notably, patients receiving the highest dosage (1800 mg/day) exhibited significant improvement in residual macular cone function, suggesting that NAC may enhance visual performance by attenuating oxidative stress in the diseased retina (Campochiaro et al., 2020).

These promising findings laid the foundation for the ongoing NAC Attack trial, a large, multicenter, and long-term clinical study planning to recruit patients worldwide (NCT05537220). This trial aims to assess the sustained efficacy and safety of prolonged NAC administration in RP, with the primary goal of slowing disease progression and preserving cone-mediated vision.

Conversely, the critical importance of endogenous antioxidant defenses in maintaining retinal integrity has been illustrated in murine models genetically deficient in SOD1, one of the key enzymes responsible for detoxifying superoxide radicals. Mice lacking SOD1 exhibit exacerbated oxidative damage and a significantly accelerated rate of cone photoreceptor degeneration compared to wild-type controls (Dong et al., 2006). Cone degeneration in rd1 mice is delayed by transgenic overexpression of SOD1 and GPx4, enzymes that catalyze the dismutation of superoxide (O_2^-) and hydrogen peroxide (H_2O_2), respectively (Usui et al., 2011). The therapeutic potential of antioxidant gene delivery has been shown in vivo: the transcription factor NRF2, which upregulates detoxifying and antioxidant genes in response to oxidative stress, can be delivered using an AAV vector to promote cone survival in rd1, rd10, and Rhodopsin$^{-/-}$ mice (Xiong et al., 2015), with positive effects on the viability of these cells.

These observations reinforce the notion that oxidative stress is not merely a byproduct but a driver of cone degeneration in RP and underscore the therapeutic potential of strategies aimed at bolstering antioxidant defenses.

4.3. *Inflammatory stress*

Central nervous system (CNS) inflammation can be broadly defined as a coordinated and multi-phase immune response occurring within the brain, spinal cord, and retina. It is characterized by the activation of resident glial cells, the recruitment of peripheral immune cells, and the release of pro-inflammatory mediators, including cytokines, chemokines, and reactive oxygen species. As such, inflammation and oxidative stress are tightly interconnected processes (Mahmoud et al., 2021). Similar to other tissues, inflammation in the CNS is typically initiated in response to injury, infection, autoimmunity, or neurodegeneration, with the primary biological goal of restoring homeostasis. However, when this response becomes dysregulated or persistent, it may lead to tissue damage and neurotoxicity.

A central feature of CNS inflammation is cellular activation, particularly the transformation of microglia and astrocytes from homeostatic to reactive states. This shift is driven by molecular signaling cascades and is characterized by the upregulation of inflammatory mediators, including key cytokines (e.g., IL-1β, TNF-α) and chemokines.

CNS inflammation exhibits both protective and detrimental properties. On one hand, it plays an essential role in the clearance of cellular debris and pathogens, thereby supporting neuroprotection and tissue repair. On the other hand, when chronic or improperly regulated, inflammation can contribute to the progression of neurodegenerative diseases, such as Alzheimer's, exacerbating neuronal loss and functional decline (Stephenson et al., 2018; Zhang et al., 2023; Adamu et al., 2024).

A critical aspect of CNS inflammation is the alteration of barrier integrity, particularly of the blood–brain barrier (BBB) and the blood–retinal barrier (BRB) (O'Leary and Campbell, 2023; Yang et al., 2020). During inflammatory episodes, these barriers often become more permeable, allowing the infiltration of peripheral immune cells. In severe or chronic conditions, structural disruption may occur, leading to excessive permeability and compromised tissue integrity (Napoli and Strettoi, 2023).

This process underscores the dual nature of CNS inflammation: while transient, controlled inflammation can be protective, persistent or dysregulated inflammation may exacerbate tissue damage. Glial activation, the release of cytotoxic molecules, and barrier breakdown all contribute to this shift from beneficial to harmful outcomes.

Under normal physiological conditions, the BRB, closely resembling the BBB, acts as a selective interface between the bloodstream and the retina, tightly regulating the access of immune cells and the exchange of molecules. In response to acute stressors such as injury or infection, temporary and regulated increases in barrier permeability can serve an adaptive role, promoting immune surveillance and tissue repair.

This controlled disruption facilitates the entry of peripheral immune cells, like monocytes and T cells, into the retina, particularly when resident microglia require reinforcement. The influx of serum proteins and growth factors can support pathogen clearance and promote recovery.

From an evolutionary perspective, transient and reversible barrier permeability likely evolved as a rapid and adaptive response to acute challenges. This process stands in contrast to the chronic, uncontrolled barrier leakage associated with many pathological states. Therefore, barrier disruption and the accompanying cellular responses in the CNS should not be viewed as inherently pathological. Rather, they represent tightly regulated processes that, under normal conditions, contribute to CNS, and by extension, retinal resilience.

5. When the eye burns quietly: unveiling retinal inflammation in RP

Numerous studies over many years have confirmed the presence of systemic anti-retina antibodies in patients with RP and established a correlation between the severity of immune and inflammatory responses and disease progression. Recent transcriptomic analyses on animal models have shown that retinal degeneration in this disease is accompanied by significant upregulation of multiple inflammatory genes (Uren et al., 2014; Guadagni et al., 2019; Bielmeier et al., 2021; Zhou et al., 2023; Ahluwalia et al., 2024). The extensive loss of large numbers of rod photoreceptors triggers a robust immune response primarily driven by resident macroglial and microglial cells, along with infiltration of circulating macrophages. In the retina, resident microglia form two distinct plexa in the outer (OPL) and inner plexiform layers (IPL), with a sparser distribution in the ganglion cell layer (GCL). Under normal conditions, microglia maintain a stable network through their ramified processes. Although traditionally considered quiescent, resting microglia are actively involved in immune surveillance and synaptic homeostasis, in the retina as elsewhere in the central nervous system (CNS). Ablation studies in adult mice have demonstrated that retinal microglia can be replenished by cells migrating from the optic nerve, which then proliferate and integrate into the local environment, suggesting that the adult retina remains receptive to immune cell recolonization (Li et al., 2019; Santos et al., 2008; Silverman and Wong, 2018). Despite their shared origin, retinal microglia display morphological and molecular heterogeneity that depends on their laminar localization and is likely influenced by extracellular signals. For example, microglia in the IPL rely on CSF1–IL–34 signaling, a dependency not observed in the OPL counterpart (O'Koren et al., 2019). Importantly, microglia ablation in adult mice disrupts retinal architecture and leads to a reduction in electroretinogram (ERG) b-wave amplitude (X. Wang et al., 2016; Li et al., 2020). In response to injury or stress, microglia adopt a reactive phenotype characterized by an amoeboid morphology, increased migratory activity, and enhanced phagocytic, antigen-presenting, and pro-inflammatory functions, depending on the molecular context. This microglia-initiated process is further amplified by infiltrating monocytes (Yu et al., 2020). Genetic deletion of *Ccr2*, a critical factor in monocyte recruitment, reduces immune cell infiltration and delays photoreceptor

loss in rd10 mice (Guo et al., 2012). Elevated levels of inflammatory cytokines and chemokines have been detected in both ocular fluids and serum of RP patients. Increased serum levels of IL-8 and RANTES correlate with decreased visual function, suggesting that systemic inflammation contributes to retinal degeneration (Tao et al., 2024). A recent study demonstrated that circulating inflammatory monocytes contribute to cone cell death in the rd10 mouse model of RP, as experimental reduction of these cells leads to a decreased rate of cone degeneration (Funatsu et al., 2022). Recent data show that the disruption of the blood-retinal barrier (BRB) during RP progression facilitates the infiltration of peripheral leukocytes—including monocytes, macrophages, and T cells—into the retinal parenchyma, demonstrating a loss of retinal immune privilege and exacerbating inflammation (Mohan et al., 2022).

Importantly, both retinal neurons and RPE cells can express immune-modulatory molecules (e.g., FasL, TRAIL-Rs, CTLA-2α, PDL-1) that help eliminate or reprogram immune cells thereby mitigating immune-mediated damage (Du and Yan, 2023; Forrester and Xu, 2012; Yu et al., 2020; Zhu et al., 2023). The initial response of microglia and infiltrating monocytes can be neuroprotective, as these cells release trophic factors such as TGF-β, BDNF, and GDNF. However, sustained neurotoxic conditions characterized by elevated levels of TNFα, IL-1β, CCL2, and CCL3 are indicative of later stages, driving cone degeneration and retinal remodeling (Du and Yan, 2023; Forrester and Xu, 2012; Yu et al., 2020; Zhu et al., 2023). Of note, in line with the initial protective role of inflammatory responses (likely debris clearance or trophic support functions), complete depletion of retinal microglia might worsen cone loss. The final goal of targeting inflammatory responses should be to modulate them. Indeed, in mouse models of RP (e.g., rd1, rd10), systemic or intravitreal administration of minocycline (a tetracycline antibiotic with microglia-modulating properties) reduces microglial activation, as seen by lower expression of Iba1, CD68, and inflammatory cytokines (e.g., TNF-α, IL-1β) and delays photoreceptor death, including both rods and secondary cone loss (Peng et al., 2014; Wang and Cepko, 2022). Overall, the retinal immune response in RP and the specific role of microglia, reflect a highly complex biological process that transcends simple binary classifications of microglial activation and warrants further experimental investigation (Sarici et al., 2023; Zhao et al., 2022). The immune response in RP may be further complicated by the influence of the gut microbiota, which interacts with immune cells within the gut-associated lymphoid tissue (GALT). Systemic inflammation and circulating microbial products have the potential to compromise blood-retinal barrier (BRB) integrity, thereby permitting infiltration of immune cells and inflammatory mediators into the retina, which can initiate or exacerbate retinal inflammation (Xu and Chen, 2022).

Within this context, a relevant role is played by Müller glial cells. These cells, strategically distributed across the entire retinal thickness, are robust responders to retinal injury (Devoldere et al., 2019; Güngör Kobat, 2020). Upon activation, Müller cells undergo hypertrophy, upregulate glial fibrillary acidic protein (GFAP) expression (Chen et al., 2022), and secrete factors that regulate microglial activation and migration, thereby shaping the local inflammatory milieu through microglia–macroglia crosstalk—an essential axis within the retinal neuroinflammatory network. Müller cells contribute to the inflammatory cascade by producing chemokines and cytokines that recruit and modulate immune cells, exacerbating inflammation in the outer retina and contributing to photoreceptor degeneration (Rutar et al., 2015).

Gene expression profiling of Müller cells in RP models reveals extensive transcriptional reprogramming, characterized by increased expression of genes involved in immune modulation, oxidative stress response, and cell survival (Roesch et al., 2012). These alterations indicate a shift toward a reactive phenotype wherein protective and deleterious functions coexist, positioning Müller cells as both sensors and amplifiers of inflammation in the degenerating retina. Restoration of Müller cell homeostasis may therefore be pivotal for photoreceptor preservation. In teleost fish, injured Müller glia possess regenerative capacity, reprogramming into multipotent progenitors capable of replacing lost photoreceptors (Lahne et al., 2020; Salman et al., 2021; Agarwal et al., 2023). Although such regenerative responses are absent in mammals, comparative studies may elucidate key mechanisms to induce similar plasticity within the mammalian retina.

6. Charting the clinical landscape of RP therapy: a synthesis

A wide range of therapeutic strategies is currently under investigation to cure, mitigate the severity or limit the progression of the RP phenotype. These include gene therapy, biomedical engineering approaches such as the development of photosensitive retinal implants, and cell-based techniques involving the transplantation of stem cells into the retina to replace lost photoreceptors. In parallel, pharmacological interventions aim to modulate the secondary pathogenic mechanisms triggered by the primary degeneration of rod photoreceptors, thereby slowing disease progression.

Among these approaches, gene augmentation therapy, which involves delivering a functional copy of the defective gene to retinal cells, has achieved clinical success and is currently the most effective strategy in restoring visual function in patients, particularly those affected by Leber Congenital Amaurosis (LCA). To date, less than 200 patients with LCA, plus several forms of RP, have been treated with gene therapy, a significant achievement that nonetheless represents only a small fraction (about 1 in 10,000) of the global RP estimated patient population. This disparity underscores the current limitations of gene-specific therapies, despite their remarkable efficacy, as outlined below.

7. The power of gene therapy

Ocular gene therapy has rapidly advanced from proof-of-concept studies to clinical trials by exploiting the unique advantages of the eye, including its easy accessibility, relative immune privilege, and the possibility of using the contralateral eye as a control. Genes linked to autosomal recessive diseases, or those that result in null genotypes, have been the focus of treatment efforts for those forms of IRDs, which benefit from supplementing a gene to produce a functional protein. Luxturna (Voretigene Neparvovec) is a preparation approved in 2017 by the U.S. Food and Drug Administration as a gene augmentation therapy for patients with biallelic missense or nonsense mutations in the RPE65 protein (retinal pigment epithelium-specific 65 kDa protein), a key component of the visual cycle. Luxturna was developed through over 15 years of successful treatment of RPE65 mutant patients and raised hopes for gene augmentation techniques to treat other monogenic IRDs (Keeler and Flotte, 2019; Y. Wu et al., 2023). The Adeno-Associated Virus serotype 2 (AAV2) was selected because of its broad tropism, low immunogenicity, and acceptable safety profile. Long-term follow-ups of treated patients have shown sustained visual improvements, albeit with some decline over time, allowing the development of new information about transgene durability (Botto et al., 2022; Y. Liu et al., 2024). Following this success, clinical trials have expanded to target a wider array of RP-associated genes. Several Phase I/II/III trials (e.g., by MeiraGTx/Janssen and AGTC) are ongoing using AAV8 or AAV9 vectors to target the RPGR gene (involved in X-linked RP). Interim results indicate stable or improved visual acuity and retinal sensitivity, with manageable adverse events. Currently targeted RP-causing genes in gene-therapy trials include (but are not limited to) RPGR, GUCY2D, XLRS, and CRB1. However, many genes leading to RP, such as USH2A, ABCA4, and EYS, cannot fit the AAV vector, which shows a packaging capacity of approximately 5.0 K) thus limiting the possibility of using this (well-experimented) vector for targeting those genes (Botto et al., 2022).

Another limitation of the gene augmentation approach is the frequent use of exogenous promoters to drive gene expression, which carries the risk of DNA methylation and progressive decline in transgene expression over time. Most importantly, gene augmentation therapy

requires identification of the causative gene mutation and the development of a tailored viral vector for each specific condition, necessitating a separate clinical trial for every individual mutation, hampering scalability.

To overcome these limitations, ongoing preclinical studies focus on employing the delivery of genes to enhance processes and pathways acting downstream of the mutation. Some gene therapy strategies have been developed to induce retinal expression of neuroprotective, antioxidant, or anti-inflammatory factors for prolonging the lifetime of photoreceptors (Xue and Cepko, 2024). The aim is to target downstream disease mechanisms common across multiple genetic subtypes. A promising approach is the AA-VV-based delivery of rod-derived cone viability factor (RdCVF), leading to an ongoing clinical trial (NCT05748873) targeting patients with RHO, PDE6A, or PDE6B mutations who retain residual cone structure, with the goal of bursting cone revitalization and survival. Preclinical studies have shown that expressing RdCVF or CNTF (ciliary neurotrophic factor) can preserve retinal structure and function in degenerating retinas. This type of approach is promising for late-stage RP, where extensive photoreceptor loss renders gene replacement unfeasible but protection of existing photoreceptors highly valuable. Critical challenges remain in defining optimal viral dosage, ensuring adequate transduction of target cells (e.g., cones, Müller glia), and avoiding off-target or immune responses. Even for these approaches, large-scale studies are still necessary to control the correct dosage of the virus, its cellular diffusion, and tropism, while long-term follow-ups are essential to validate safety and efficacy, especially when chronic expression of therapeutic transgenes is required. And yet, the field of gene therapy has made impressive progress.

Genome editing has emerged as a transformative approach for correcting dominant mutations and those involving large genes that cannot be replaced using conventional AAVs (Hsu et al., 2014; Yan et al., 2023; Geiger et al., 2025). The CRISPR-Cas9 system has shown great promise in correcting RP-associated mutations in preclinical models (e.g., Pde6b in rd10 mice), leading to restored protein expression and partial recovery of visual function. However, clinical translation of CRISPR-Cas9 is still in its infancy for ocular applications. Key challenges include delivery precision, minimizing off-target effects, and managing potential immune responses to the bacterial Cas9 protein. No CRISPR-based RP gene therapies have yet entered clinical trials, although programs are advancing toward first-in-human studies (notably for CEP290 in Leber congenital amaurosis, via Editas Medicine).

Anti-sense Oligonucleotides (ASOs) represent another promising class of gene-targeted therapeutics. These short, synthetic nucleic acid sequences (typically 15–30 nucleotides) hybridize with pre-mRNA or mRNA to modulate splicing, degrade transcripts, or inhibit translation. Unlike DNA-based gene editing, ASOs do not cause permanent genomic changes and do not introduce double-stranded breaks, thereby offering a potentially safer alternative. ASOs are particularly suitable for dominant-negative mutations, splicing defects, and mutations affecting large genes unsuitable for viral delivery trials (Paunovska et al., 2022; Wang et al., 2020; Xue and MacLaren, 2020). Several ASO therapies for RP are advancing in clinical trials.

Recent molecular genetic approaches are based on modifying the RNA to fix splicing errors (such as Sepofarsen, technically a splice-modifying antisense oligonucleotide) or to suppress toxic, gain-of-function mutations (like QR-1123, which allows the allele-specific knockdown of mutant mRNA): the first is designed for LCA10 (Russell et al., 2022) and the second for RHO mutations ("Dominant RP: FDA Designation"), with other approaches in preclinical or early-phase clinical development. Their repeatable dosing and potential for titration offer additional clinical flexibility, as they provide non-viral, repeatable, and localized treatment approaches for retinal diseases, an alternative to gene editing or AAV-based delivery in some cases (Crooke et al., 2021; Girach et al., 2022; Takeshima, 2025).

As a result, the gene therapy pipeline has expanded to encompass a diverse array of strategies, including gene augmentation, genome editing, and optogenetics, alongside gene-independent approaches targeting broader biological processes. This diversification reflects the underlying heterogeneity of RP, indicating that a combination of therapeutic modalities will likely be required to effectively address this complex disorder.

Ongoing efforts are focused on developing gene-agnostic treatments, including those employing viral vector systems designed to bypass the need for a specific genetic diagnosis. However, these remain largely at the preclinical stage and are not yet available in clinical settings. Despite notable advances, a universal, broadly applicable therapy for RP remains an unmet goal.

8. Prostheses to restore vision

The now-discontinued Argus II retinal prosthesis was among the first "bionic eye" systems to restore partial vision in patients with advanced retinal degeneration, operating through electrical stimulation of the inner retina. This pioneering technology spurred the growth of a broader field that now includes retinal, optic nerve, and cortical implants, all designed to deliver visual signals to the brain. Devices like Argus II interface directly with residual retinal circuitry, delivering patterned electrical stimulation to various components of the visual pathways to evoke visual percepts in individuals who are blind or severely visually impaired (Mills et al., 2017; Hallum and Dakin, 2021; Ramirez et al., 2023).

A particularly promising frontier in this field is the development of organic retinal prostheses, which offer an alternative to conventional electronic implants. These systems utilize organic semiconducting polymers and photoactive pigments to achieve neural stimulation, offering key advantages such as enhanced biocompatibility, mechanical flexibility, and compliance with delicate retinal tissue (Maya-Vetencourt et al., 2017; Manfredi et al., 2019). Materials explored to date include a variety of polymer formulations and photoactive compounds, each with differing levels of functional stability and biological integration (Ohayon and Inal, 2020). For instance, fully organic devices constructed on silk fibroin substrates and functionalized with photoactive polymer layers have been successfully implanted in animal models and are currently undergoing preclinical and early-phase clinical evaluation (Guidetti et al., 2022; Brooks and Yadavalli, 2025).

Most retinal prosthetic devices are surgically implanted either subretinally, beneath the remaining retinal layers, or within the space previously occupied by the degenerated photoreceptor and retinal pigment epithelium (RPE) complex, or epiretinally, adjacent to the retinal ganglion cell (RGC) layer. While devices that have progressed to human implantation have enabled some patients to regain rudimentary visual abilities, such as light perception, motion detection, and spatial localization, their clinical utility remains limited by several significant technical and biological challenges (K. Y. Wu et al., 2023b; Menia and Venkatesh, 2025).

Current prostheses typically provide low spatial resolution, as the number of stimulating electrodes remains far below the density of photoreceptors in a healthy retina. Surgical implantation is invasive and carries risks such as retinal detachment, hemorrhage, and infection. Moreover, postoperative adaptation to artificial visual input varies widely among individuals and can be cognitively demanding. Additional limitations include electrode degradation, battery life constraints, and long-term biocompatibility concerns.

Despite these challenges, retinal prostheses remain a compelling and mutation-agnostic therapeutic option for individuals with end-stage retinal degeneration. Their potential to bypass damaged retinal circuitry, and even the entire eye, offers a pathway for treating a broader range of vision-threatening conditions beyond RP. Ongoing research aimed at improving resolution, enhancing material biocompatibility, refining surgical approaches, and reducing costs holds promise for expanding their clinical applicability.

9. Mutation-agnostic therapies: from the bench

An interest in developing gene-agnostic therapies, potentially treating a wide spectrum of IRD genotypes, has been developed over the years. Classical studies based on pharmacological approaches, beginning with vitamin supplements and administration of trophic factors, have progressed to include anti-oxidants, inhibitors of microglia, and drugs directed toward the central nervous system (CNS), leading to as many clinical trials, which, however, have rarely met expectations. Recently, more modern efforts have restored interest in these approaches. Broadly, these approaches rely on general or local administration of molecules which target: (i) neurotrophic support (e.g., CNTF, RdCVF; NGF); (ii) maintenance of the visual cycle (e.g., retinoid analogs, vitamins); (iii) mitigation of oxidative stress (e.g., N-acetylcysteine, various antioxidants); (iv) enhancement of metabolic resilience (e.g., mTOR modulation, insulin signaling); and (v) suppression of inflammation (e.g., minocycline, microglial inhibitors). While many of these agents demonstrated promising results in preclinical models, only a few, such as CNTF and N-acetylcysteine, have progressed to clinical evaluation, with ongoing trials assessing their efficacy in preserving cone function (Fortuny and Flannery, 2018; K. Y. Wu et al., 2023a; Bighinati et al., 2024).

An intrinsic challenge of these interventions is that none constitute a definitive cure; most act to slow disease progression rather than restore lost vision. Consequently, demonstrating measurable improvements in standard endpoints, such as best-corrected visual acuity (BCVA), as required by regulatory authorities, is inherently difficult, since visual decline in RP typically occurs gradually and over long periods. Nevertheless, even modest deceleration of disease progression can be highly meaningful, effectively prolonging the functional lifespan of photoreceptors otherwise destined for degeneration.

The concept of the existence of intrinsic factors released from the eye and necessary for survival of other cells, born with studies of retinal development, has led to the identification of the already mentioned Rod-derived cone viability factor (RdCVF), an endogenous molecule secreted by rods and capable of activating the metabolism of cones, promoting their survival in various animal models of RP; this has led to an ongoing clinical trial (NCT0574887). for patients with rod-cone dystrophies of different genetic origin, and based on AA-VV delivery (by subretinal injection) of genetic material aimed at increasing RdCVF production.

Other examples of clinical trials promoting photoreceptor survival in a mutation-agnostic manner target widespread biological processes accompanying the progression of RP: the mentioned NAC Attack clinical trial is based on the administration of N-acetyl cysteine, a potent anti-oxidant that reduces oxidative damage, for mitigating the progression of RP. The same molecule is being used by a Phase 3 Clinical trial launched by Johns Hopkins University, in which NAC is used for the treatment of RP for its powerful anti-inflammatory activity. Minocycline is another drug in a clinical trial as an immunosuppressant to limit microglial cell activation.

These preclinical and clinical studies, further described below, rely on targeting generalized processes that accompany RP independently of the underlying genetic defect and that might provide effective therapeutic tools for the majority of affected individuals, prolonging the lifetime of retinal cones.

10. Anti-apoptotic strategies

The activation of intrinsic apoptotic pathways is central to many forms of photoreceptor degeneration. Accordingly, early therapeutic strategies aimed to counteract apoptosis. One of the first and most studied approaches involved overexpression of Bcl-2, a regulator of mitochondrial membrane permeability and apoptosis inhibition (Wenzel et al., 2005). Transgenic models expressing human Bcl-2 under photoreceptor-specific promoters showed delayed degeneration and preserved retinal function in both light-induced and genetic models (Chen et al., 1996; T. Chen et al., 2024).

Subsequent studies targeted upstream or parallel pathways of apoptosis. Ceramide, a pro-apoptotic sphingolipid also studied in cancer biology, was found elevated in degenerating retinas. Its pharmacological reduction via myriocin, a serine palmitoyltransferase inhibitor, preserved photoreceptor structure and function in RP mouse models (Piano et al., 2020; Platania et al., 2019; Strettoi et al., 2010). Like other anti-apoptotic strategies, ceramide targeting aims to delay, rather than halt, degeneration. Efforts have also included gene therapy, small-molecule inhibitors, and peptides targeting caspases, XIAP, and neurotrophic pathways (Leonard et al., 2007; Y. Wu et al., 2023; Yao et al., 2012).

Despite initial promise, enthusiasm for anti-apoptotic therapies has waned due to challenges in delivery, safety, and limited efficacy. Apoptosis is only one of several cell death pathways in RP. Necroptosis, pyroptosis, parthanatos, calpain overactivation, and dysregulated autophagy also contribute (Brunet et al., 2022; Campochiaro and Mir, 2018; Zhuang and Chen, 2020). Some are linked to TNFα or oxidative stress; others, like autophagy, can be protective or harmful depending on context (Chang et al., 2022). Thus, therapies solely targeting apoptosis may provide incomplete or temporary protection.

Moreover, many RP-causing mutations affect essential photoreceptor functions, such as phototransduction or ciliary trafficking, resulting in persistent stress and dysfunction even when apoptosis is blocked. For example, some RHO mutations cause rhodopsin misfolding, triggering ER stress, CHOP upregulation, and caspase-independent death via apoptosis-inducing factor (AIF) (Chang et al., 2022; Sanges et al., 2006).

By contrast, PDE6 mutations impair cGMP breakdown, leading to calcium overload, activation of the intrinsic apoptotic pathway, calpain activation, and structural disintegration. Calpains and Histone Deacetylases (HDAC) promote further nuclear changes, while PARP overactivation depletes energy stores, driving necrosis or apoptosis (Comitato et al., 2020; Forman and Zhang, 2021). Notably, HDAC inhibitors effectively restored part of photoreceptor function in rd10 mice, pointing to the potential of epigenetic therapies (Samardzija et al., 2021; Dong et al., 2023; Carullo et al., 2024).

These findings highlight that different mutations activate distinct degenerative pathways, complicating universal anti-apoptotic strategies. Additionally, indiscriminate apoptosis inhibition risks prolonging the survival of dysfunctional cells, potentially worsening inflammation or impairing retinal homeostasis. Therefore, anti-apoptotic approaches are best viewed as adjuncts to gene therapy, neuroprotection, or regenerative strategies. Durable photoreceptor preservation will likely require combined therapies targeting both genetic defects and downstream degenerative cascades.

11. Neurotrophic factor-based therapies

Several neurotrophic factors are currently under investigation for their potential to slow retinal degeneration. Among them, Brain-Derived Neurotrophic Factor (BDNF) and Glial cell line-Derived Neurotrophic Factor (GDNF) have garnered significant attention (Blouin et al., 2024). BDNF primarily supports retinal ganglion cells and inner retinal neurons, enhancing synaptic plasticity and offering protection to secondary neurons following photoreceptor loss (Kimura et al., 2016; Zhang and Qu, 2023). In contrast, animal model studies have shown that GDNF acts directly on photoreceptors, promoting their survival by means of activation of the GFRα1/RET receptor complex (Frasson et al., 1999; Sanftner et al., 2001). However, both BDNF and GDNF exhibit short half-lives and poor ocular bioavailability when delivered systemically. To overcome these limitations, adeno-associated viral (AAV) vectors are commonly employed to achieve sustained intraocular expression (Dalkara et al., 2011). The Pigment Epithelium-Derived Factor (PEDF) is an additional promising candidate due to its combined neurotrophic, antioxidant, and anti-angiogenic properties. Endogenously secreted by the RPE, PEDF has been shown to protect photoreceptors, reduce

oxidative stress, and modulate microglial activation in degenerating retinas (Jakobsen et al., 2024). Gene therapy strategies designed to enhance PEDF expression have demonstrated efficacy in preclinical models (Askou et al., 2019; Qiu et al., 2025).

A recent investigation explored the efficacy of "painless" Nerve Growth Factor (hNGFp), a recombinant form of the well-known NGF engineered to lack allogenic effects while retaining anti-inflammatory properties and microglia-inhibitory activity (Capsoni et al., 2012, 2017; Malerba et al., 2015). hNGFp was tested for possible photoreceptor neuroprotection and retinal anti-inflammatory action in the rd10 mouse model of RP, by intraocular delivery across the time window of maximum photoreceptor death. Despite a strong rationale for its use in an RP model, hNGFp failed to rescue cone photoreceptors in rd10 mice in the experimental conditions chosen. This limited efficacy may be attributed to insufficient bioavailability at the target site as well as insufficient NGF receptor expression on the target cells (photoreceptors and microglia) and/or different properties of retinal microglia (Napoli et al., 2024).

While, in general, preclinical studies of neurotrophic factors have shown encouraging results, their clinical translation remains challenging. Major obstacles include achieving sustained and cell-type-specific delivery, addressing inter-individual variability due to the genetic heterogeneity of retinal diseases, and accounting for fundamental differences between retinal and remaining central nervous system environments. Moreover, neurotrophic therapies are largely protective rather than regenerative, as they may slow degeneration but do not restore lost photoreceptors or reverse vision loss. Consequently, future therapeutic strategies will likely require combination approaches. Integrating neurotrophic support with gene therapy, anti-inflammatory agents, or cell replacement techniques may enhance efficacy. Advancing this field will depend on refining delivery systems, improving targeting specificity, and identifying patient subgroups most likely to benefit from these interventions.

12. Photobiomodulation

A recent therapeutic strategy for cone preservation in inherited retinal diseases, including RP, is photobiomodulation (PBM). Also referred to as low-level laser therapy, PBM involves the application of low-energy red to near-infrared light to the retina, with the aim of enhancing mitochondrial metabolism and attenuating oxidative stress (Geneva, 2016). In RP, PBM has demonstrated potential to preserve cone function by improving bioenergetics, reducing oxidative damage, and modulating inflammatory responses, thereby addressing key mechanisms underlying the bystander effect and delaying secondary cone degeneration following rod loss. The proposed mechanism is based upon the ability of specific wavelengths to target mitochondrial chromophores, like cytochrome C oxidase, preserving mitochondrial redox state (Gopalakrishnan et al., 2020). Early pilot studies involving small patient cohorts have reported transient visual improvements, suggesting that repeated or sustained treatment may be required to maintain therapeutic benefit. Importantly, PBM was generally well tolerated in these studies (Siqueira, 2024). An exploratory clinical trial is currently underway at University College London (NCT06224114), evaluating the effects of colored-light exposure delivered via a hand-held torch on cone contrast thresholds (CCT) in adults with RP.

13. Keeping the lights on: glucocorticoids for saving cones

A wide range of pharmacological agents, including small molecules, classical anti-inflammatory drugs, and genetic interventions, have been employed in preclinical models to suppress microglial activation, particularly in central nervous system (CNS) disorders characterized by prominent inflammatory components. In Alzheimer's disease, for instance, secondary neuroinflammation has emerged as a therapeutic target in ongoing clinical trials aiming to inhibit inflammasome activity, reduce CD3 cytokine levels, or modulate microglial reactivity. These strategies reflect a growing consensus that neuroinflammation plays a central role in the pathogenesis and progression of neurodegenerative diseases (Zhang et al., 2023; Giri et al., 2024).

Glucocorticoids (GCs), among the most potent anti-inflammatory agents, are widely used in both systemic medicine and ophthalmology (Gaballa et al., 2021). In ophthalmic practice, they are frontline therapies for non-infectious uveitis, are commonly administered post-operatively following cataract or retinal surgery, and are essential in managing conditions such as thyroid eye disease and scleritis.

Recent advances in drug delivery have enabled the development of sustained-release implants and gene therapy vectors designed to optimize the therapeutic efficacy of GCs while minimizing adverse effects, including elevated intraocular pressure and cataract formation.

In the retina, GCs are primarily indicated for conditions with a clear inflammatory component, such as retinal vein occlusion (RVO) and cystoid macular edema, both of which may also arise as complications of RP. Additionally, their ability to downregulate vascular endothelial growth factor (VEGF) and inflammatory cytokines has made them attractive adjuncts to anti-VEGF therapies in age-related macular degeneration (AMD), although GCs are not typically used as monotherapy for this condition.

Despite their established role in treating inflammatory retinal disorders, GCs have not been widely adopted for retinal degenerations like RP. Nevertheless, preclinical studies suggest their potential. For example, treatment with fluocinolone acetonide has been shown to protect photoreceptors and reduce microglial activation in rodent models of RP (Glybina et al., 2010). Building on this evidence, we investigated the therapeutic potential of dexamethasone in the rd10 mouse model of RP, which harbors a mutation in the rod-specific phosphodiesterase gene (Pde6b) and undergoes a typical rod-cone degeneration.

14. Preclinical studies with GCs on rd10 mutant mice

Dexamethasone is a potent synthetic glucocorticoid with strong anti-inflammatory and immunosuppressive effects, long-lasting activity, and minimal mineralocorticoid action compared to other corticosteroids. It can be administered systemically (oral, intravenous, or intramuscular) or locally (topical, periocular, or intravitreal), and is widely used in ophthalmology for various inflammatory and vascular conditions (Gaballa et al., 2021).

Because of its well-characterized pharmacokinetics, ability to cross the blood-retinal barrier, and established anti-inflammatory properties, we hypothesized that systemic dexamethasone administration could reduce retinal inflammation and protect cone photoreceptors from secondary (bystander) degeneration. The relevance of inflammatory responses to cone degeneration was supported by numerous studies and by transcriptomic analysis, which highlighted the upregulation of inflammatory genes during the peak of cone degeneration (Guadagni et al., 2019).

Hence, we administered subcutaneous dexamethasone to rd10 mice from postnatal day 24–45 (P24–P45), a critical window during which rod photoreceptor death peaks and cones begin to die. Indeed, we achieved a conspicuous rescue of cones (30 % rescue) and a comparable functional preservation of visual acuity and contrast sensitivity in photopic conditions.

In the retina of treated mice, dexamethasone significantly reduced inflammation, as evidenced by decreased expression of molecular markers associated with microglial activation and inflammatory signaling. Histological and functional assessments confirmed the preservation of cone photoreceptor structure and cone-mediated visual function, indicating that dampening inflammation can mitigate secondary cone degeneration in RP (Guadagni et al., 2019). This study underscores the importance of inflammation in cone degeneration and lays the groundwork for developing safer, targeted anti-inflammatory

therapies involving glucocorticoids, which may hold promise for preserving photopic vision in RP patients.

15. Intraocular dexamethasone to rd10 mice: new data

Aware of the perspective difficulties of a clinical translation based on daily administration of systemic GC to RP patients, we tested the effect of ocular dexamethasone implants in rd10 mice using a modification of Ozurdex, a preparation of semi-solid dexamethasone patented by Allergan in 2008 (here referred to as "Dexa"). Ozurdex is inserted into the vitreous of patients under surgical conditions. It is used in patients with ocular inflammatory processes, such as macular edema, uveitis, and cataract, and results in a sustained release of the glucocorticoid for several months. Implants were obtained from Ozurdex (or control) ophthalmological preparations, which were cut under a dissection microscope into 4 identical fragments of less than 2 mm, from the original 7-mm implants (Fig. 3). Surgery did not cause evident adverse effects to the mouse eyes, which healed quickly and maintained shape and corneal and lens clarity throughout the time of observation. Ocular pressure, tested at surgery and at the time of eye removal, was unaltered. The implant gradually dissolved, although an imprinting was usually visible on the retina of mice at 45 days, when their eyes were dissected. Controls were littermates that received an identical implant devoid of dexamethasone.

A quantitative analysis demonstrated the effects of the implant on cone survival and microglia cells organization through immunostaining and image acquisition with a structured-light, fluorescence microscope, carried on across the whole retinal extension to take into account the typical center-to-periphery degeneration pattern (Fig. 4 A). Immunofluorescence staining with cone-arrestin antibodies of whole-mounts and retinal sections showed that retinas treated with Dexa exhibited significantly better preservation of cones than controls in terms of numbers and structure (Fig. 4B–G). Cones in treated retinas had longer outer segments (Fig. 4D and E), although the parent cells had remodeled, appearing shortened and bent as typically seen in retinal degeneration. Systematic counting confirmed that the survival rate of cones was, on average, 30 % higher than in controls (Fig. 4B–E). No survival effect was detected for rods, which had largely degenerated by the end of the chosen observational window, as shown by the number of ONL rows in vertical sections. Hence, intraocular Dexa successfully preserved 30 % of all cones in rd10 mice, a significant fraction of these cells, and at a rate comparable to that achieved with systemic (daily) administration of the same drug in the same mouse model.

The limited availability of dexamethasone and control preparations, combined with the delicate ocular surgery required in this study, constrained the number of animals that could be used. Consequently, we did not perform functional analyses, as these would have required additional anesthesia and carried a risk of mechanical damage to the retina.

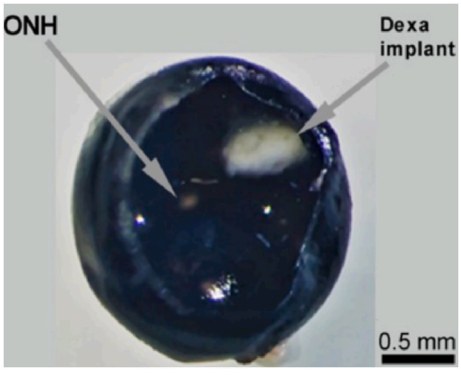

Fig. 3. Implant of dexamethasone (Dexa) in the mouse eye. The eye cup shows an implant of about 1.2 mm size, photographed the day after the insertion. ONH: optic nerve head.

Instead, we prioritized tissue collection for molecular assays. Importantly, previous studies employing diverse pharmacological and environmental interventions have consistently shown a strong correlation between cone survival and preservation of ERG responses (Barhoum et al., 2008; Carullo et al., 2024; Gargini et al., 2007; Guadagni et al., 2015; Strettoi et al., 2010; Yang et al., 2024). Future experiments will be dedicated to including functional assays.

In the same retinal samples used for cone survival assessment, inflammatory responses were investigated by immunostaining of microglia. Activated microglial cells in the outer retina, distinguishable by their amoeboid, globose morphology (Fig. 5A–E), can be reproducibly counted in retinal whole-mounts stained for Cd11b or Iba-1, confining the analysis to the outermost plexus, located in the photoreceptor layer (Fig. 5D–E). In dexamethasone-treated retinas, microglial cells were less numerous than in controls. They occupied an intermediate position in the outer nuclear layer, without reaching the RPE/photoreceptor border as they do in the maximally activated state.

16. Glucocorticoids and protection of the RPE

Glucocorticoids are known to rescue the integrity of different types of barriers, including the inner retinal barrier, by directly modulating tight-junction expression and/or indirectly inhibiting the secretion of metalloproteases (Felinski et al., 2008; Fischer et al., 2014; Salvador et al., 2014; Van Der Wijk et al., 2019).

The integrity of the RPE in rd10 mice implanted with Dexa was assessed by examining the profile of the regulatory protein Zonula Occludens 1 (ZO-1), which plays a fundamental role in tight junction homeostasis, by RPE immunostaining with ZO-1 antibodies. Structured-light microscopy and image analysis using an ad hoc developed, custom-made software (Happythelium) allowed a quantitative assessment of RPE preservation. It is known that interruptions in ZO-1 profiles in the RPE are associated with the breakdown and leakage of the outer retinal-blood barrier, which accompanies RP-like abnormalities in various mouse mutants (Napoli et al., 2021). RPE specimens from Dexa-treated mice retained a higher continuity compared to controls, with a statistically significantly lower number of interruptions in ZO-1 stained profiles (Fig. 6A–D). Additionally, the perimeter and area of individual RPE cells, automatically measured in RPE whole mounts, were smaller, leading to a statistically higher cell density (cells/mm^2) (Fig. 6D). The eccentricity of individual RPE cells, low in cases of morphological regularity, did not differ between treated and control groups. Hence, this analysis showed preservation of the main RPE parameters in Dexa-treated eyes.

RPE whole mounts in rd10 mutants also demonstrated the presence of large cells, which could be stained with Iba1 and CD11b antibodies, located on the choroidal side of the RPE, and observed to elongate thin processes penetrating toward the retina. These large cells of the immune system contained ZO-1 positive intracellular fragments, suggestive of phagocytosis of ZO-1 components of RPE cells (Fig. 7A) and immune infiltration from the choroidal side of the retina (Fig. 7B).

Dexamethasone exerts its action through binding to the Glucocorticoid Receptors (GS) (Escoter-Torres et al., 2020; Vettorazzi et al., 2022), whose precise retinal localization is somewhat controversial. Immunostaining on samples from wild type mice with anti-GR antibodies demonstrated the presence of GR in multiple cell types in the retina, with evident staining of the membrane of rods and cones, as well as of INL cells, and cellular profiles occupying the position of Müller cells (Fig. 8A and B). RPE cells exhibited evident staining of cell membranes and nuclei (Fig. 8C and D), particularly evident in central areas, close to the optic nerve head.

The distribution of GR staining suggests that the effects of dexamethasone on photoreceptor survival and RPE preservation might be both direct and indirect, through the action of other retinal cell types (i.e., Müller cells). Indeed, the molecular inflammatory profile obtained by qRT-PCR after subcutaneous dexamethasone administration to rd10

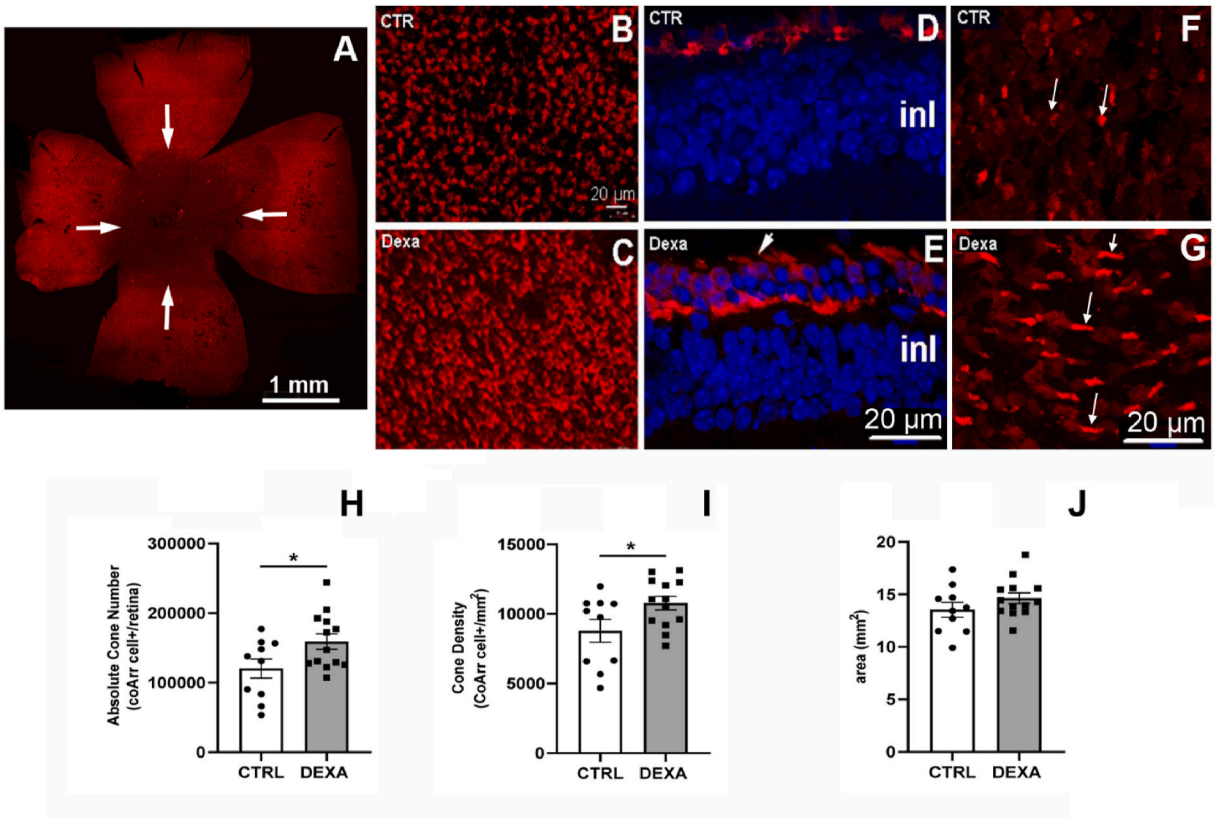

Fig. 4. Dexa intraocular implant and cone rescue. A: Cone staining with arrestin antibodies (red signal) in a retinal whole mount from a mouse of the rd10 strain. At this age (45 days), the central retinal area is already largely devoid of cones and shows a weak residual staining for cone arrestin (arrows). High magnifications of retinal whole mounts (**B, C**) with the same staining show that cones are more numerous in **C** (Dexa) than in **B** (control) case. **D, E**: Retinal vertical sections, with cone arrestin (red), and nuclear staining (blue), highlighting the higher preservation of cones (longer and more numerous) in Dexa-treated (**E**) compared to control mice (**D**). INL: inner nuclear layer. **F, G:** High magnification of cone outer segments stained with arrestin antibodies in retinal whole mounts. Arrows point to scant and short outer segments in the control case (**F**) as opposed to the more numerous, longer and brighter profiles visible in the Dexa treated sample (**G**). **H, I**: Cone number quantification shows that these cells are 30 % more numerous in Dexa samples (**H**, Ctrl = 11, Dexa = 13; unpaired *t*-test, two-tailed; p = 0.0330). Their density is also higher (**I**, Ctrl = 11, Dexa = 13; unpaired *t*-test, two-tailed; p = 0.0395) in Dexa-treated retinas compared to controls. **J:** The area of individual retinal samples did not differ between the two experimental groups (Ctrl = 11, Dexa = 13; unpaired *t*-test, two-tailed; p = 0.2101). Error bars are ±SEM, and symbols represent individual cases; *p = 0.05.

mice during the P24-P50 time window shows a decrement of typical macro and micro-glia-inflammatory genes, indicative of a direct action on the cells of the immune system.

RT-PCR assays for GR on wild type retinas demonstrated a stable expression from P25 to adulthood (Fig. 8E and F) and thus across the period of photoreceptor degeneration we analyzed. Overall, the distribution of GR staining suggests that the effects of dexamethasone on photoreceptor survival and RPE preservation might be direct, and/or acting through other retinal cell types (i.e. Müller cells).

17. Glucocorticoids: more than inflammation modulators?

As previously discussed, glycolytic deprivation has been implicated in cone photoreceptor vulnerability and progressive central vision loss in RP. Remarkably, direct delivery of glucose into the subretinal space has been shown to restore outer segment synthesis and cone function, underscoring the critical role of metabolic support in cone survival (W. Wang et al., 2016).

Under physiological conditions, glucocorticoids may offer metabolic benefits to cones beyond their anti-inflammatory effects. These hormones can enhance mitochondrial function by promoting oxidative phosphorylation and increasing ATP production through the upregulation of mitochondrial enzymes(Kuo et al., 2015; Kokkinopoulou and Moutsatsou, 2021). In parallel, glucocorticoids stimulate systemic gluconeogenesis, raising circulating glucose levels, which could be advantageous for cones via enhanced glucose uptake through transporters such as GLUT1 and GLUT3. By reducing inflammation, glucocorticoids also suppress microglial activation and decrease the production of pro-inflammatory cytokines (e.g., TNF-α, IL-1β), indirectly shielding cones from inflammatory damage (Ingawale and Mandlik, 2020; Stifel et al., 2022; Auger et al., 2024).

Metabolic effects of glucocorticoids on photoreceptors and RPE cells have not been studied in great detail. Injections of dexamethasone have been shown to prevent light-induced apoptosis of photoreceptors in Balb-c mice by activation of GR receptors and inhibition of the activator protein AP-1 activity (Wenzel et al., 2001). Dexamethasone protects human RPE cells from oxidative stress and decreases the oxidation rate of glutathione (Nuzzi et al., 2016). Recent studies show that dexamethasone protects ARPE-19 cells from oxidative insults caused by H_2O_2 exposure (see Supplementary Fig. 1), a property also shared by recently synthesized analogs (Di Marco et al., 2025).

As already discussed, numerous studies demonstrate a direct increase in hematic glucose following glucocorticoid administration. This effect, *per se*, could contribute to rescuing cone photoreceptors, demonstrated to suffer from starvation (Petit et al., 2018). Still, the cascade of molecular changes mediating this possible action, likely following GR binding, is not known. A likely hypothesis follows the combination of studies demonstrating a) that glucocorticoids stabilize the factor HIF1alpha (Vettori et al., 2017), a master regulator of glucose metabolism, by enhancing the transcription of glucose transporters (GLUT1)

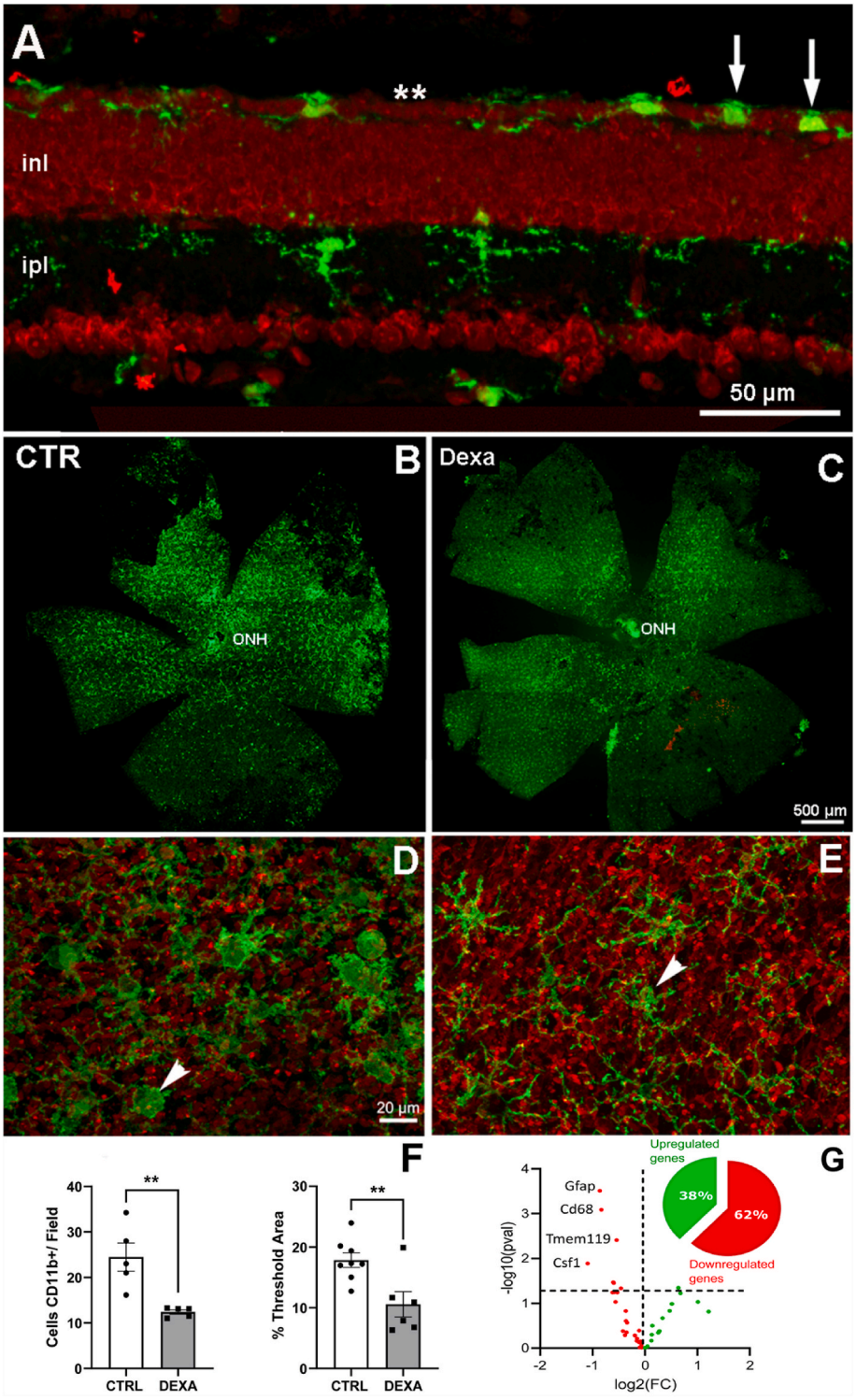

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Fig. 5. Dexa implants attenuate the retinal inflammatory profile. **A:** vertical section of rd10 mouse retina with Iba1 staining of microglia (green) and nuclear counterstaining (red). Activated microglial cells of amoeboid shape (arrows) have migrated to the outer retina, at the RPE border. The microglial plexus of the inner plexiform layer (ipl) has remained quiescent and highly ramified. **B, C:** retinal whole mounts, Cd11b staining of microglia shows clustering of cells across the entire retinal surface in CTR retinas; microglial cell density is lower and staining milder in Dexa-treated samples (**C**). The focus is on the outer retina. **D, E:** high magnification of preparations shown in **C** and **D**, highlighting the intermingling of microglial and cone photoreceptor processes (red, cone arrestin staining) in the outer retina. Arrowheads point to amoeboid cells in D and more ramified cells in E (Dexa-treated sample). **F:** Diagrams of numbers of Cd11b positive cells in Ctrl and Dexa-treated retinal samples show that the population of microglial cells is 30 % denser in control cases. (Ctrl = 8, Dexa = 6; unpaired *t*-test, two-tailed; Left diagram: p = 0.0049. Right diagram: p = 0.0073). Data are shown ±*SEM;* symbols represent individual cases; **p = 0.01. **G:** Vulcano plot of qRT-PCR data from retinal extracts obtained from rd10 mice (n = 5 treated with Dexa and 4 controls) treated with 0.4 mg/gr subcutaneous Dexa during the P25-P45 interval, in a time window identical to the one used for mice implanted with Dexa intraocularly. The significant downregulation of genes typically associated with micro- and macroglial reactivity (Gfap, Tmem19, Cd68, Csf1) fits with the pharmacological, anti-inflammatory profile of Dexa. Additional relevant genes are reported directly in the graph. The percentage of genes up- and down-regulated is referred to all the analyzed genes. The horizontal dashed line divides the genes with a significant change (up to the line, p < 0.05) from the non-significant ones.

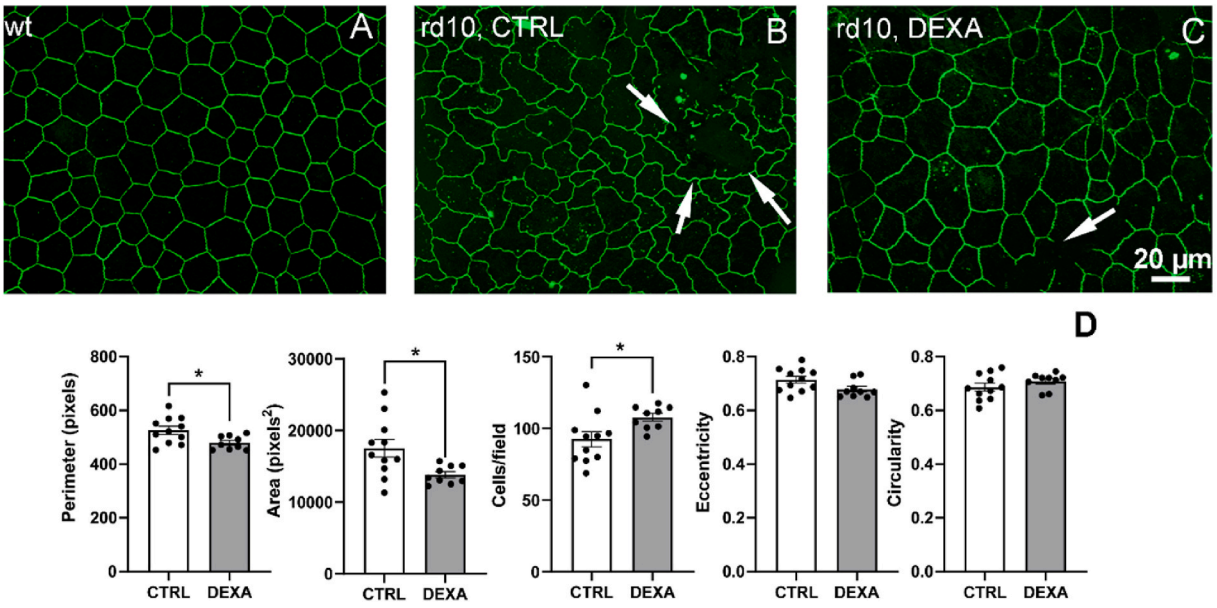

Fig. 6. Effects of Dexa on the RPE. A-C: whole mount preparations of the RPE from wild type (**A**) and rd10 (**B, C**) mice. Staining with antibodies against ZO-1, a regulatory protein of tight junctions (green). Ruptures in the tight junctions are seen as large discontinuities in ZO-1 profiles (arrows), absent in the wild type (**A**) and numerous in the rd10 (**B**). Treatment with Dexa reduces considerably the number of ZO-1 interruptions (**C**). **D:** Quantitative analysis of ZO-1 profiles shown in the diagrams demonstrates a lower perimeter and a large average area of ZO-1 polygons, with a higher number of polygons ("Cells") per unit area upon Dexa treatment. The "Eccentricity", or irregularity of ZO-1 polygons, is unvaried (ctrl = 11, Dexa = 9; unpaired *t*-test, two-tailed; perimeter, p = 0.0200; area, p = 0.0189; cells/field, p = 0.0266; eccentricity, p = 0.0524; circularity, p = 0.257). Error bars represent ±SEM, and symbols represent individual cases.

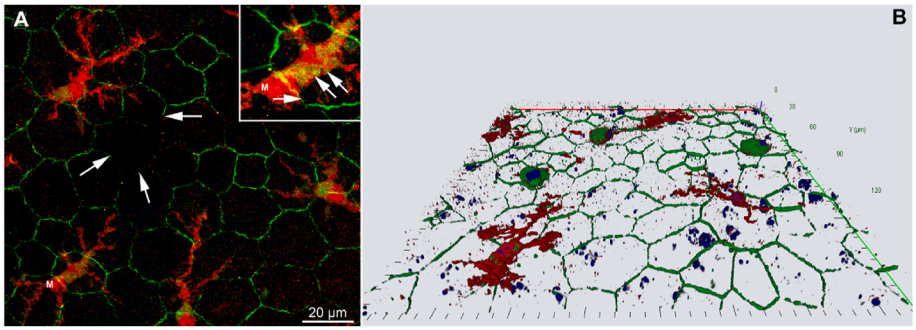

Fig. 7. Immune cells on the outer side of the RPE. A: Iba 1 labeling of large cells of the immune system lining the outer side of the RPE shows that discontinuities in ZO-1 staining (arrows) coincide with the presence of ZO-1 positive residues inside these immune cells (inset), suggesting they had phagocyted components of the RPE junctional complexes. **B.** Rendering of an analogous image after computer rotation, illustrating the close relation between Iba1-positive (red) cells and the tiling of ZO-1-positive, RPE profiles.

and glycolytic enzymes such as hexokinase II, pyruvate dehydrogenase kinase and PKM2 (Lum et al., 2007; Kierans and Taylor, 2021); and that b) genetic stabilization of HIF1alpha in rd10 mice increases cone survival by reprogramming the altered equilibrium of glucose in the retina and RPE (Caruso et al., 2025). Hence, glucocorticoids could support cone metabolism by glucose reprogramming, altered by RP phenotype progression.

Taken together, these observations suggest that glucocorticoids may

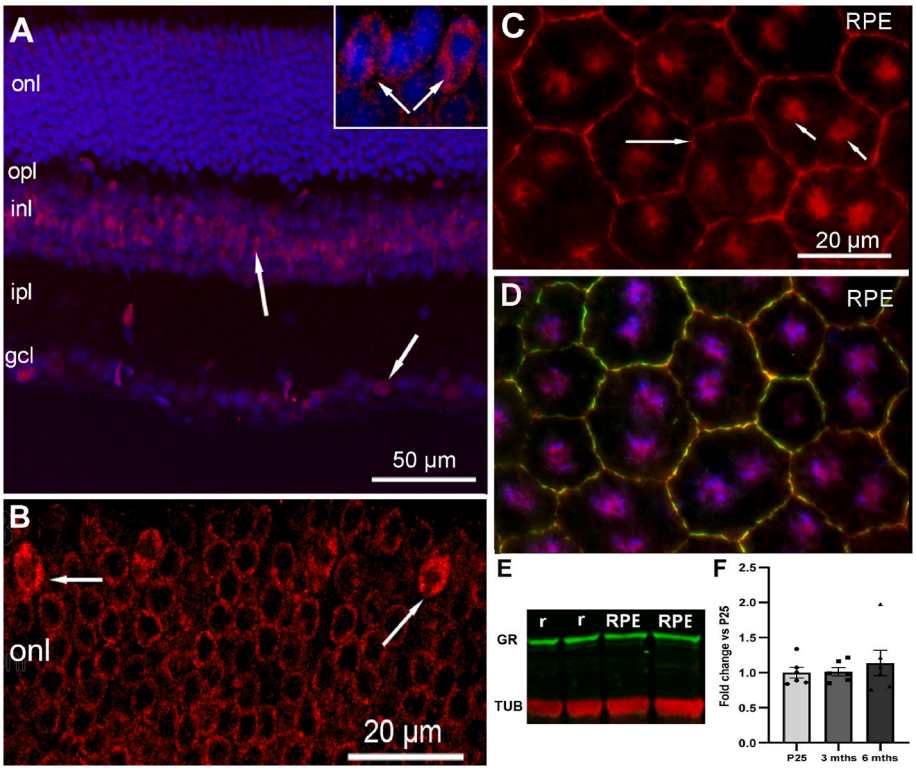

Fig. 8. Glucocorticoid receptor (GR) distribution in the retina and the RPE. Immunostaining for GR (red signal) in the retina **(A, B)** and the RPE **(C, D).** Blue: nuclear counterstaining. Labeled photoreceptors and inner retinal cells (arrows) are evident in **A**. Arrows in the inset in **A**, and in **B** point out to cones. Arrows in **C** show the membrane-related and nuclear pattern of GR expression in the RPE. **D**: co-staining for ZO-1 (green) shows RPE cell profiles. **E:** Western blot from retinal extract ("r") and RPE show abundant expression of GR in both preparations. Tub: tubulin. **F**. Quantification of GR expression at different ages (P25, n = 6; 3 months, n = 6; 6 months, n = 6). Ordinary one-way ANOVA, p = 0.6809). Error bars represent ±SEM, symbols represent individual cases.

protect cones not only through immunomodulation but also via direct metabolic and antioxidant mechanisms. While these pathways remain incompletely studied in the retina, they open compelling avenues for further research into the multifaceted roles of glucocorticoids in neuroprotection.

Future studies might reveal whether the bystander death of cones could be limited by attenuating only the initial (strongest) phase of retinal inflammation, corresponding to the peak of rod death and massive microglial recruitment, exploiting the ability of brief exposures to glucocorticoids to raise the capacity of mitochondria to generate energy to resist acute stress (Spiers et al., 2015; Obrador et al., 2023). The complex pharmacological properties of dexamethasone and the large number of genes modulated by this drug suggest that the observed rescue of cones might be due to a combination of factors, which includes a systemic effect on glucose metabolism. It is known that a fundamental glucocorticoid effect is to preserve plasma glucose for the brain during conditions of stress (Jaszczyk and Juszczak, 2021). "Starving" cones in RP depend heavily upon glucose, and a higher availability of sugar might help to support their survival.

To our knowledge, this is the first report of a highly successful cone rescue in RP rodents achieved using a widely employed corticosteroid implant, which has been in ophthalmology since 2009. Indeed, a pilot study on human RP patients implanted with Ozurdex to limit inflammatory reaction associated with cataract surgery reported maintenance of the Ellipsoid Zone (EZ) in High Density OCT examination, highly suggestive of cone preservation (Savastano et al., 2024). Measurements of best-corrected visual acuity (BCVA) revealed an improvement both in RP patients implanted intraocularly with Ozurdex and in controls; however, the limited sample size precluded further statistical elaboration. However, the measurable preservation of the ellipsoid zone (EZ) following Ozurdex implantation provides structural evidence of cone survival. The EZ hyperreflective band is generated by the aligned foveal cone inner segments, a cellular region critically enriched in mitochondria and therefore highly relevant to cone physiology (Kar et al., 2023; Tao et al., 2016). Notably, no adverse effects were reported in the RP patients who received the implant.

Our findings highlight the potential for repurposing of this well-known corticosteroid as a partial solution to the current lack of pharmaceutical treatments for RP and underline the importance of preserving photoreceptors in expectation of a definitive therapy.

18. Conclusions

The observed 30 % cone rescue rate obtained with either systemic or local dexamethasone is second only to insulin administration, which previously showed superior efficacy and supports the repurposing of this drug as a promising strategy to slow RP progression. Importantly, this strategy is both novel and feasible, leveraging an established, cost-effective drug with a well-characterized pharmacological profile. The repurposing of systemic medications for ophthalmic use has precedents; for instance, metformin, commonly used in type 2 diabetes, has shown potential in reducing the risk of dry age-related macular degeneration (AMD), as observed in epidemiological studies of diabetic patients. A similar rationale may apply to dexamethasone. Given that steroid tolerability testing is standard practice in ophthalmology clinics, patients at risk for steroid-induced complications, such as ocular hypertension, can be identified and excluded from treatment.

As RP is a chronic and progressive condition requiring long-term management, repeated intravitreal dexamethasone implants may be necessary to maintain therapeutic benefit. This approach is already established in the management of diabetic macular edema and in trials mentioned below. Looking ahead, the development of longer-acting implants and next-generation glucocorticoid derivatives, such as those combining anti-inflammatory and antioxidant properties (Di Marco

et al., 2025), may further enhance the specificity and durability of treatment for RP. The beneficial effect of dexamethasone on RPE preservation is particularly significant, given the critical role of this layer in supporting photoreceptor homeostasis and viability and may hold therapeutic potential beyond RP. Recent findings (J. Liu et al., 2024) demonstrate that restoring molecular immunomodulation within the RPE mitigates dysregulated inflammation in experimental models of AMD, promoting photoreceptor survival. These observations suggest that fundamental protective mechanisms may extend beyond disease boundaries, providing a broader framework for retinal neuroprotection.

In contrast to other agents considered for cone preservation, such as certain neurotrophic factors, dexamethasone introduces specific safety considerations inherent to steroid therapy. Among ocular implants, the most notable risks are elevated intraocular pressure and cataract formation. Elevated pressure can be effectively managed by pre-screening patients via dexamethasone sensitivity testing, while cataract, although a concern in the already vulnerable RP eye, frequently arises in this disease independently of Ozurdex implantation. Importantly, long-term experience with Ozurdex in other ocular conditions, including repeated implants over periods exceeding three years, has demonstrated a favorable safety profile with minimal serious adverse events, as reported in MEAD, NCT 00168337 and 00168389 clinical trials and by the number of trials and studies employing this drug (Kim et al., 2015; Bandello et al., 2018). Taken together, these findings underscore a compelling rationale for repurposing dexamethasone in RP, warranting the design of a dedicated clinical trial to evaluate its efficacy in this context.

The time seems ripe to explore such interventions in the hope of offering patients a much-needed means to preserve vision.

19. Methods

The following sections refer to dexamethasone intraocular experiments and related original data.

Study approval. All experimental procedures conformed to the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research and were approved by a protocol authorized by the Italian Ministry of Health (authorization N. 350/2023-PR) and by an institutional ethical committee (OPBA-CNR).

Animals. Mice were B6 CXB1-Pde6b^{rd10}/J, rd10, homozygous for the phosphodiesterase (Pde) mutation, and C57Bl6 (wild type, wt) mice, all originally from the Jackson Laboratory (Bar Harbor, ME USA). Animals were kept in a 12 h light/dark cycle facility with an illumination level below 50 Lux. A number of 26 rd10 mice were used for implant studies (15 with Dexa and 11 with a control preparation). Of these, 2 Dexa and 1 control animals were excluded for post-surgical ocular problems. All retinal preparations from the implant mice were used for histological studies. An additional group of 12 rd10 mice were used for subcutaneous studies; of these, 6 were injected with dexamethasone and 6 with control solution. All mice were implanted intraocularly or injected with Dexa at 25 days of age (P25) and harvested at P45. Implants, injections and eye removal were done under deep Zoletil anesthesia. Additional C57Bl6 mice (wild type, wt) were sacrificed at P25 (n = 6), P90 (n = 6) and P180 (n = 6) and their retinas were isolated for real-time PCR. A group of 8 wt mice, P90, were used for retinal Western Blot analysis. All groups were gender balanced; an analysis separated as a function of sex was not performed as was not considered as a biological variable. Experimental design. For long-term administration of Dexa in the eyes of rd10 mice, we utilized Ozurdex®, an Allergan-patented formulation of solid polymer containing 700 μg of dexamethasone, designed for injection into the vitreous of patients' eyes i.e., with macular edema or uveitis, biodegraded over 3–4 months (40). We fractionated the 7 mm barrels of the original Ozurdex preparation into seven identical 1 mm fragments, each containing 100 μg of the drug. The fragments were individually injected into the eyes of rd10 mice aged 25 days (P25), near the corneal margin, using the original device's pen-like scalpel (Fig. 3). The mice were harvested at P55, thus exposing them to the drug during the P24-P50 peak period of rod-cone degeneration. Control mice were intraocularly injected with a 1 mm barrel of biodegradable polymer containing no Dexa. At 45 days, mice were enucleated under deep Zoletil anesthesia and euthanized.

Immunohistochemistry. The retinas and retinal pigment epitheliums (RPEs) were isolated and processed for immunocytochemistry (ICCH) as whole mounts to visualize cones, microglia, and RPE junctional complexes (ctr = 10, Dexa treat = 13). Antibodies for retinal preparations were anti-Cone Arrestin (ab15282, Millipore Sigma, MA, USA); anti-CD11b (ab8878, M1/70 Abcam, Cambridge, UK), anti-Iba-1 (anti-ionized calcium-binding adapter molecule 1) (019–19741, Wako, Rimini, Italy). Secondary antibodies were donkey anti-rabbit-Alexa Fluor-568 (cat.n. A-11011, Invitrogen, Thermofisher Scientific, Waltham, MA, USA) and donkey anti-rat-Alexa Fluor-488 (cat.n. 712-546-153, Jackson Immuno Research Laboratories, West Grove, PA, USA). RPE preparations were stained as whole mounts using antibodies against Zonula occludens 1 (ZO-1, MABT11, Merck-KGaA, Darmstadt, Germany) and Iba-1. Nuclear counterstaining was done with micromolar concentrations of DAPI or Hoechst (Sigma-Aldrich, Merck SpA, Milan, Italy). Some fixed eyecups were frozen in dry ice and cold isopentane and sectioned vertically on a cryostat at 13–15 μm, collected on slides, and treated with the same antibodies as above. Additional wild-type retinal samples and RPE preparations were used to reveal the distribution of glucocorticoid receptors (GR) using a rabbit monoclonal antibody (Clone D8H2, Cell Signaling Technologies Inc., Danvers, MA, USA).

Microscopy and imaging. Images of the retina and RPE whole mounts were acquired with a Zeiss Imager.Z2 Microscope equipped with an Apotome3 device (Carl Zeiss, Oberkochen, Germany), using a Plan Neofluar 40X, NA 1.25 oil objective or with a Zeiss Laser Scanning (LSM) 900 Confocal Microscope (Carl Zeiss, Jena, Germany), using a 40X/1.4 Plan-Apochromat oil objective. For cell counting purposes, retinal whole mounts with cone-arrestin and CD11b staining were sampled along 4 radial axes, at 2 mid-peripheral and 2 central locations with the Imager 7.2 microscope. A total of 16 sampling fields were imaged/retina; each field was a z stack of serial optical sections at 2 μm intervals encompassing the whole width of the outer nuclear; additional stacks were obtained across the whole ONL to acquire microglial cells. Scanning fields were 125 × 125 μm for cone acquisition and 250 × 250 μm for microglia. Cell counts were performed navigating through the z stack on a high-definition monitor and scoring each cell with the cell counting tool of Metamorph. A total number of cones was obtained by multiplying average cellular densities for corresponding retinal areas, measured in bright field by low power microscopy. RPE flat mounts labeled by ZO-1 antibodies were imaged along the 4 radial axes, imaging 20–24 fields per sample, using the Zeiss Imager.Z2 microscope. Maximum projections, bidimensional images, were obtained from single z-stacks and used to quantify the continuity of ZO-1 profiles using a home-made script, as detailed in Supplementary Information.

RNA extraction and quantitative PCR for genes of retinal inflammatory reaction Animals treated with 0.4 mg/gr subcutaneous Dexa or saline during the P25-P45 interval, a time window similar to the one used for mice implanted with Dexa intraocularly, were used to investigate the retinal molecular profile by Real-Time PCR. Homogenates from rd10 retina aged P45 (n = 6 from dexamethasone injected and n = 6 from control rd10 mice) were used for RNA extraction with a RNeasy Mini Kit (Qiagen, Hilden, Germany) according to the producer's indications. The RNA concentration of each sample was determined through a NanoDrop 2000 C Spectrophotometer (ThermoFisher Scientific, MA, USA). cDNA synthesis was achieved by using the RT2 First Strand Kit (cat.n.330401, Qiagen; Hilden, Germany) and gene expression was performed on customer RT2 ProfilerTM PCR Arrays. A Step One Plus machine (ThermoFisher Scientific, MA, USA) was utilized to conduct and monitor each Real-Time PCR step. The Step One Plus

program automatically determined the quantitative values for cDNA amplification based on the threshold cycle number (Ct) that was achieved during the exponential expansion of the PCR products. The RT2 ProfilerTM PCR Array Data Analysis Template from Qiagen was applied for data analysis on Real-time-PCR arrays. A volcano graph displaying the log2(fold change) of each gene versus its -log10(p values) was generated to show the results. Genes analyzed in the arrays: csf1, gfap, cd68, vegfa, slc2a1, arg1, lamp2, itgam, tmem119, mtor, myod88, mrc1, stat3, tsc22d3, map1lc3a, ccl5, nfkb1, il12a, foxp3, aif1, cd4, c1qa, c3, cxcl12, tgfb1, il18, cd40, l1b, cd19, il4, ccl3, hif1a, cd8a, ccl2, casp1, nos2, il17a, ccr2, tnf, ifng, il10, il2, il6. Housekeeping genes: gadph, actb. The QuantiTeck Reverse Transcription Kit (cat.n.205311, Qiagen; Hilden, Germany) was used in combination with single gene expression Taqman assays to assess the expression of the glucocorticoid gene, nr3c1 (Mm0043332_m1), in wt animals at different ages.

Western Blot. A total of n = 8 RPEs and retinas from wild-type (C57Bl6/J strain) mice, aged 50 days, were used. Proteins were extracted and 25 μg protein loaded and electrophoresed on a 4–12 % Bis-Tris Criterion XT Precast gel (BioRad, Milan, Italy) and blotted on a 0.2 μm nitrocellulose membrane with a semidry transfer system (Trans-Blot Turbo; BioRad). The nitrocellulose membrane was blocked in the Odyssey blocking buffer (LI-COR Bioscience, Lincoln, Nebraska, USA), for 2 h, RT and incubated overnight at 4 °C with the same anti-Glucocorticoid receptor antibody used for immunofluorescence and with mouse anti-α tubulin (Sigma-Aldrich, mouse monoclonal clone B-5-1-2) for reference. Secondary antibodies conjugated to IRDye 680LT or to IRDye 800CW were Goat Anti-Rabbit IgG (diluted 1:5000) or Goat Anti-Mouse IgG (diluted 1:10000) (Li-Cor Biosciences, Lincoln, NE, USA). The reaction was detected by an Odyssey IR scanner and acquired by Image Studio software v5.2 (Li-Cor Biosciences).

Statistics. Data from Dexa-treated and control groups were compared using an unpaired *t*-test. The significance value was set ≤ 0.05. Data were evaluated with GraphPad 8.0.2, also used to generate illustration graphs. Diagrams (graphical abstract and schemes of Figs. 1 and 2) were designed with the aid of SciDraw free software.

19.1. HAPPYthelium, a free script for RPE quantification

This is a Matlab, computer-vision application, designed for segmenting objects. Initially, the app filters an image of RPE to remove small circular objects using multilevel image thresholds with Otsu's method and morphological operations. Afterward, it reconstructs an RGB image, which is then processed using k-means clustering with two groups, to differentiate the signal from the background. The cluster representing the signal is used to create a binary mask. This mask undergoes multiple dilations with directional structuring elements, followed by skeletonization and the removal of small objects to enhance segmentation quality. Subsequently, all objects within the binary mask are labeled using 4-connectivity, and their region properties are calculated using Matlab's regionprops function. These properties include the centroid, area, perimeter, eccentricity, orientation, and circularity of each labeled region. The area of a region is defined as the total number of pixels within the region's boundaries. The perimeter is determined by summing the lengths of all boundary edges. Eccentricity, a measure of how elongated a region is, is defined as the ratio of the distance between the foci of the region's best-fit ellipse to its major axis length, with values ranging from 0 (a perfect circle) to 1 (indicating highly elongated shapes). Orientation is the angle between the major axis of the best-fit ellipse of a region and a reference axis (usually the horizontal axis), measured in degrees. Circularity, a measure of the roundness of objects, is calculated using formula 4*pi*Area/Perimeterˆ2)*(1 - 0.5/r)ˆ2 where r = Perimeter/(2*pi) + 0.5, and ranges from 0 to 1, with 1 indicating a perfect circle. Data can be represented as block diagrams or heatmaps. The app is available open source on GitHub at this link: https://github.com/raffaelemazziotti/hAPPytelium_code.

CRediT authorship contribution statement

Debora Napoli: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Beatrice Di Marco:** Visualization, Validation, Methodology, Investigation. **Giulia Salamone:** Writing – review & editing, Visualization, Methodology, Investigation, Data curation. **Noemi Orsini:** Validation, Methodology, Investigation. **Raffaele Mazziotti:** Software, Methodology, Formal analysis. **Enrica Strettoi:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization.

Study approval

All experimental procedures conformed to the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research and were approved by a protocol authorized by the Italian Ministry of Health (authorizations N. 350/2023-PR) and by an institutional ethical committee (OPBA-CNR).

Link for free download of software for image analysis https://github.com/raffaelemazziotti/hAPPytelium_code.

Declaration of generative AI and AI-assisted technologies in the writing process

Statement: During the preparation of this work the author(s) used ChatGTB in order to improve writing clarity and manuscript readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preteyeres.2025.101403.

Data availability

Source data used to generate graphs for this study are available in Excel format upon request.

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