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REVIEW

Dysregulation of histone deacetylases in ocular diseases

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Abstract

Ocular diseases are a growing global concern and have a significant impact on the quality of life. Cataracts, glaucoma, age-related macular degeneration, and diabetic retinopathy are the most prevalent ocular diseases. Their prevalence and the global market size are also increasing. However, the available pharmacotherapy is currently limited. These diseases share common pathophysiological features, including neovascularization, inflammation, and/or neurodegeneration. Histone deacetylases (HDACs) are a class of enzymes that catalyze the removal of acetyl groups from lysine residues of histone and nonhistone proteins. HDACs are crucial for regulating various cellular processes, such as gene expression, protein stability, localization, and function. They have also been studied in various research fields, including cancer, inflammatory diseases, neurological disorders, and vascular diseases. Our study aimed to investigate the relationship between HDACs and ocular diseases, to identify a new strategy for pharmacotherapy. This review article explores the role of HDACs in ocular diseases, specifically focusing on diabetic retinopathy, age-related macular degeneration, and retinopathy of prematurity, as well as optic nerve disorders, such as glaucoma and optic neuropathy. Additionally, we explore the interplay between HDACs and key regulators of fibrosis and angiogenesis, such as TGF-β and VEGF, highlighting the potential of targeting HDAC as novel therapeutic strategies for ocular diseases.

Keywords Histone deacetylase · Ocular disease · Diabetic retinopathy · Aged-macular degeneration · Glaucoma · Retinopathy of prematurity · Retinitis pigmentosa · Retinoblastoma · Optic neuropathy · VEGF · TGF-β

Introduction

Ocular disorders are a growing global issue that significantly affects quality of life. Cataracts, glaucoma, age-related macular degeneration (AMD), and diabetic retinopathy (DR) are the most prevalent ocular diseases (Foster and Resnikoff 2005), and their prevalence is expected to increase significantly in the coming decades (Tham et al. 2014; Teo et al. 2021; Deng et al. 2022). The global market size is also increasing, with an estimated annual growth rate of approximately 9.3% from 2023 to 2030 (Grand View Research Report, GVR -3-68038-766-7). However, the pharmaceutical treatment options are currently limited. For cataracts, surgery is the only available treatment (Lam et al. 2015). Anti-vascular endothelial growth factor (VEGF) antibodies have been used for AMD, DR, and ROP (retinopathy of prematurity) (Lim et al. 2012; Alagorie et al. 2021; Brown et al. 2021; Chatziralli 2021; Tan et al. 2021; Tao et al. 2021; Valikodath et al. 2021). Lastly, topical pressure-lowering medications such as prostaglandin analogs, are the first-line therapy for glaucoma (Weinreb et al. 2014).

These diseases share common underlying features like neovascularization, inflammation, and/or neurodegeneration (Capitao and Soares 2016; Baudouin et al. 2021). Histone deacetylases (HDACs) are desirable targets for studies in various research fields, notably cancer, inflammatory diseases, neurological disorders, and vascular diseases (Glauben et al. 2009; Cantley and Haynes 2013; Park et al. 2022). Understanding the function of HDACs in ocular diseases

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plays a crucial role in gaining insights into the pathogenesis and developing fundamental treatment approaches.

This review article delves into the function of HDACs in ocular diseases, with a particular focus on DR, AMD, and ROP, as well as optic nerve disorders, such as glaucoma and optic neuropathy. Furthermore, we investigate how HDACs interact with important regulators of fibrosis and angiogenesis. We evaluate how HDACs affect TGF-β and VEGF signaling and provide an interpretation within the context of ocular diseases.

HDAC classification and its dysregulation in various diseases

HDAC classification

HDACs are a class of enzymes that catalyze the removal of acetyl groups from lysine residues in histone proteins, an important component of chromatin. The deacetylation of histones results in a more compact chromatin structure that is transcriptionally inactive and can lead to gene repression. In addition to their interaction with histones, HDACs modulate non-histone proteins' acetylation status.

HDACs can be divided into two main groups based on their deacetylase domains and specific cofactors: the histone deacetylase family and the sirtuin protein family. The 18 mammalian HDACs can be further categorized into four classes: Class I (HDAC1, HDAC2, HDAC3, and HDAC8), Class II (HDAC4, HDAC5, HDAC6, HDAC7, HDAC9, and HDAC10), Class III (Sirt1, Sirt2, Sirt3, Sirt4, Sirt5, Sirt6, Sirt7), and Class IV (HDAC11). Class I, Class II, and Class IV HDACs are Zn^{2+}-containing enzymes, while Class III HDACs have a different catalytic mechanism that utilizes nicotinamide adenine dinucleotide^{+} (NAD^{+}) as a cofactor (Houtkooper et al. 2012; Ellmeier and Seiser 2018) (Fig. 1). Class I HDACs are predominantly located in the nucleus and are involved in the deacetylation of histones and non-histone proteins. They form complexes with other proteins to repress target genes (Ayer 1999). HDAC8 is an exception that functions alone without forming a large complex (Hu et al. 2000). Class II HDACs are further subdivided into Class IIa (HDAC4, HDAC5, HADC7, and HDAC9) and IIb (HDAC6 and HDAC10). Class IIa HDACs have binding sites for two important proteins:14-3-3 and myocyte-specific enhancer factor 2 A (MEF2A). These binding sites are crucial for the movement of molecules between the nucleus and the cytoplasm (Yang and Grégoire 2005). Class IIb HDACs have a characteristic tail domain at the C-terminus. HDAC6 has two deacetylase domains and a zinc finger ubiquitin-binding domain (ZnF-UBD), also known as polyubiquitin-associated zinc finger (PAZ), that plays a crucial role in transporting misfolded protein cargo to aggresomes (Yang and Grégoire 2005; Hai et al. 2017). The zinc-binding group, which is unique to HDAC6, has been the focus of intensive study for the selective inhibition of HDAC6 in the development of HDAC6 inhibitors. Chong Kun Dang Pharmaceutical has completed phase 2 clinical trials (NCT04204603) for CKD-506, a potential treatment for autoimmune diseases such as rheumatoid arthritis. Additionally, CKD-510, based on the non-hydroxamic acid structure, has completed phase 1 clinical trials (NCT04746287) and is being evaluated for its potential efficacy in treating Charcot-Marie-Tooth and atrial fibrillation. HDAC10 has a catalytic domain and a leucine-rich repeat domain (Hai et al. 2017). Class III HDACs share conserved domains and rely on NAD^{+} and peptide-binding. Sirt5, a member of the sirtuin family, has little or no deacetylase activity but can remove acyl groups from histones and proteins (Du et al. 2011; Sabari et al. 2017). The spatial expression of sirtuins is diverse. Sirt1, Sirt6, and Sirt7 are located in the nucleus, Sirt3, Sirt4, and Sirt5 are located in the mitochondria, and Sirt2 is found mainly in the cytoplasm (Houtkooper et al. 2012; Ellmeier and Seiser 2018).

Dysregulation of HDACs in various diseases

HDACs are associated with various biological processes, including gene regulation, DNA methylation, DNA repair, histone modification, chromatin remodeling, cell cycle progression, apoptosis, and development. Dysregulation of HDACs has been associated with fibrosis, angiogenesis, and inflammation and has been implicated in various diseases. Accordingly, HDACs have emerged as promising therapeutic targets for various diseases, including cancer, neurodegenerative disorders, vascular disease, and inflammatory diseases (Glauben et al. 2009; Cantley and Haynes 2013; Pedro Ferreira et al. 2021; Park et al. 2022).

Naïve $CD4^{+}$ T-cells differentiate into effector Th1 and Th2 cells in the immune system, producing IFN-γ and IL-4, respectively. In addition, IL-12 is required for differentiation into Th1 cells, whereas IL-4 is necessary for differentiation into Th2 cells. HDACs are epigenetic regulators that influence the production of various types of cytokines involved in T-cell differentiation (Bowen et al. 2008; Aune et al. 2009). IL-2 is a cytokine that plays an important role in the differentiation and development of T-cells. HDAC1 binds to the IL-2 promoter and suppresses its expression (Kametani et al. 2008). Also, in unstimulated cells, HDAC1 combines with the p50 subunit of NF-kB and suppresses downstream gene expression (Zhong et al. 2002). HDAC7 suppresses the expression of Nur77 and regulates the apoptosis rate of T-cells during T-cell receptor engagement (Dequiedt et al. 2003). Sirt1 inhibits regulatory T-cell (Treg) differentiation by controlling FoxP3, reduces oxidative stress by controlling FoxO1, and reduces inflammatory factors of macrophages (Shen et al. 2021).

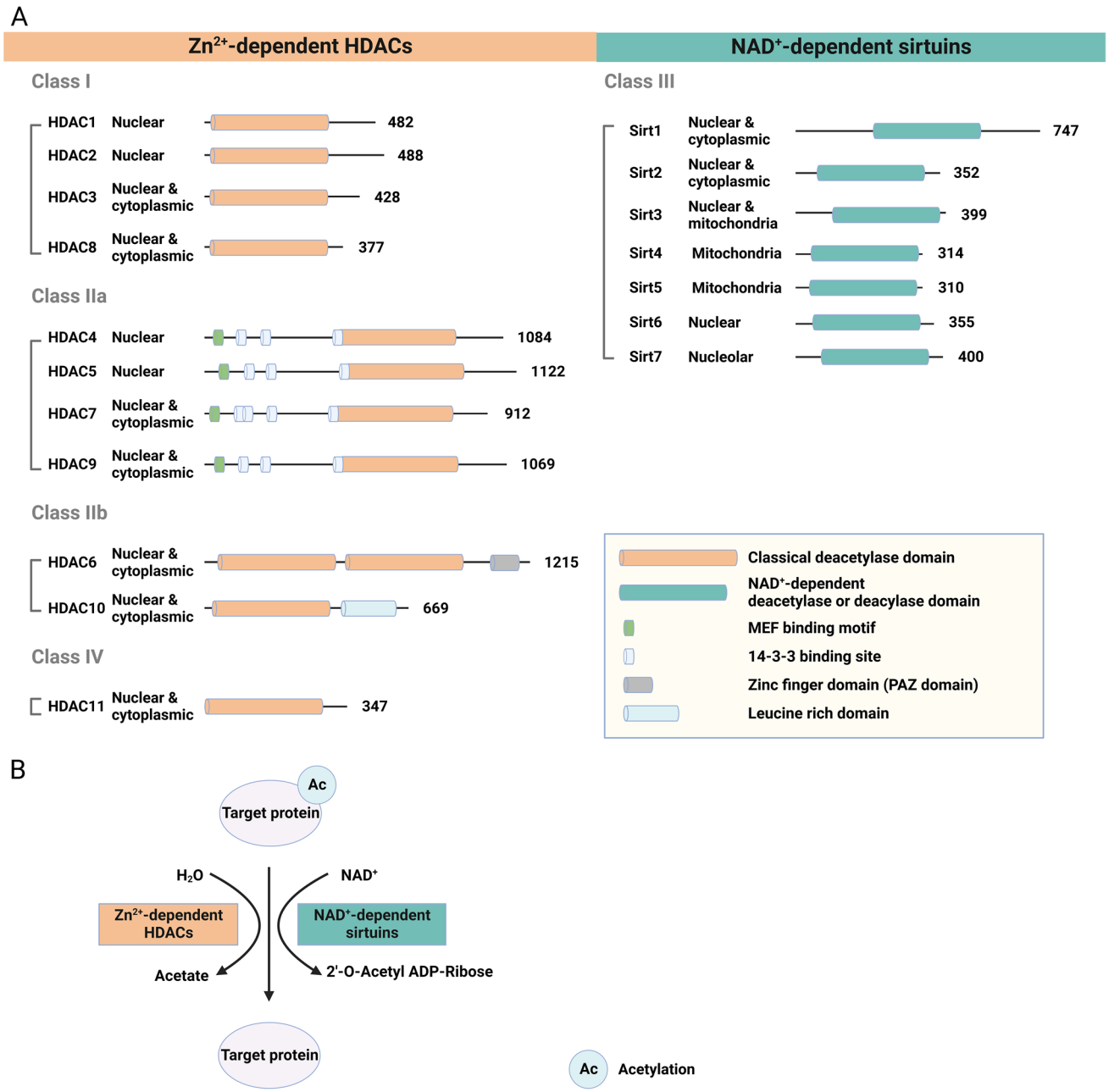

Fig. 1 Classification and catalytic mechanisms of HDACs. **A** HDACs are divided into four classes based on their structure and catalytic mechanisms. Class I, Class II, and Class IV are Zn^{2+} containing enzymes. However, Class III HDACs have a distinct catalytic mechanism that employs NAD^+ as a cofactor. The intracellular localization and the total number of amino acids for each HDAC protein are presented (Only the longest isoform is shown). **B** Both Zn^{2+} dependent HDACs and NAD^+ dependent sirtuins interact with the target protein and deacetylate the acetylation moiety. Figures were created with Biorender.com

Dysregulation of HDACs in diabetic retinopathy

DR is a disease associated with abnormal blood vessel growth in the retina and is a leading cause of vision loss in developed countries, typically occurring 10 to 15 years after diabetes diagnosis (Cheung et al. 2010; Jampol et al. 2020). The main risk factors of DR are disease duration and uncontrolled blood glucose levels. Without treatment, DR can progress from mild non-proliferative DR (NPDR) to severe NPDR or proliferative DR (PDR) (Wong et al. 2016). Recent studies have shown that treatment with antibodies against VEGF, such as ranibizumab, bevacizumab, and aflibercept, can effectively reduce diabetic macular edema and improve vision, replacing macular laser therapy as the

primary treatment (Elman et al. 2010; Michaelides et al. 2010; Mitchell et al. 2011; Nguyen et al. 2012; Brown et al. 2015; Heier et al. 2016).

Since 2015, Ranibizumab (Lucentis, Genentech) and aflibercept (Eylea, Regeneron) have been FDA-approved for diabetic macular edema. Their indications were expanded respectively to include all forms of DR in 2017 and 2019. They target all VEGF-A isoforms and prevent neovascularization by restoring retinal vascular permeability (Alagorie et al. 2021; Brown et al. 2021; Chatziralli 2021; Tan et al. 2021; Tao et al. 2021). However, the frequency and duration of treatment required for optimal results remain unclear.

Sirt1 plays a therapeutic role in DR. Retinas from experimental DR models display reduced Sirt1 expression and activity (Lamoke et al. 2015; Zhao et al. 2016; Liu et al. 2018; Ji et al. 2020; Qi et al. 2020; Hammer et al. 2021). Sirt1 overexpression (Kowluru et al. 2016; Mishra and Kowluru 2017; Mishra et al. 2018) and the pharmacological activation of Sirt1 (Kowluru et al. 2014; Sarubbo et al. 2018; Tu et al. 2021) have been found to have therapeutic effects in DR. Under DR conditions, there is a positive feedback loop involving Sirt1, Ac-p65, and miR-23b-3p. Specifically, Sirt1 deacetylates Ac-p65 on the K310 site. A reduction in Sirt1 leads to the accumulation of Ac-p65 and activates the NF-κB signaling pathway (Lanzillotta et al. 2010; Yang et al. 2012; Zhao et al. 2016). Furthermore, Ac-p65 directly binds to the promoter region of miR-23b-3p, increasing its expression. This, in turn, acts as a negative regulator of Sirt1 expression (Zhao et al. 2016). These processes explain the deterioration of symptoms due to a decrease in Sirt1 expression in DR and the positive feedback loop associated with the decline in Sirt1 expression. Sirt1 is also regulated by other miRNAs in DR, including miR-34a, miR-195, miR-204, and miR-211. AntagomiRs of these Sirt1-regulating miRNAs have shown therapeutic effects in DR (Mortuza et al. 2014; Zhao et al. 2016; Thounaojam et al. 2019; Chen et al. 2020; Ji et al. 2020; Qi et al. 2020).

Retinas from patients with DR and experimental models show increased HDAC6 levels (Abouhish et al. 2020). The activity of ERK1/2-HDAC6 has been implicated in the worsening of lesions in DR, while the administration of Glucagon-like peptide 1 has been shown to improve lesions by decreasing HDAC6 expression (Cai et al. 2017; Yuan et al. 2018). Furthermore, the HDAC6 inhibitor tubastatin A has been found to have therapeutic effects in DR models (Abouhish et al. 2020).

Sirt3 maintains retinal homeostasis, and its depletion accelerates NAD^+ reduction and disease progression in streptozotocin-induced animal models (Mao et al. 2020). Non-obese diabetic mice show reduced Sirt6 expression in the retina, and a central nervous system-specific Sirt6 KO mouse was found to accelerate disease progression (Zorrilla-Zubilete et al. 2018). Moreover, an experimental DR model showed increased expression of HDAC1, HDAC2, HDAC3, HDAC6, and HDAC8 and decreased expression of HDAC4 and HDAC5 (Zhong and Kowluru 2010; Fu et al. 2020; Che et al. 2022). Targeting HDAC3 mRNA using short-hairpin RNA has shown therapeutic effects in DR animal models (Che et al. 2022).

Dysregulation of HDACs in age-related macular degeneration

Macular degeneration results from a combination of genetics and environment, but aging is the primary risk factor. AMD can be classified into two main types: dry AMD, accounting for about 90% of cases, and wet AMD, which accounts for about 10% of cases (Flores et al. 2021). Dry AMD is characterized by the accumulation of yellowish-brown waste called "drusen" in the retina. It is usually asymptomatic and associated with a lower risk of vision loss. However, it can progress to wet AMD at any time, making early intervention crucial. Alternatively, wet AMD leads to blindness due to leakage of fluid or blood from abnormal blood vessels into the macula (Lim et al. 2012; Mehta 2015; Stahl 2020; Thomas et al. 2021). In this section, we discuss the role of HDACs in AMD pathogenesis.

Dry AMD Dry AMD is an early manifestation of AMD that is characterized by the presence of drusen between Bruch's membrane (BM) and the retinal pigment epithelium (RPE) (Bowes Rickman et al. 2013). While the precise mechanism of drusen formation remains unclear, several factors have been implicated, including genetic elements related to complement, lipid, and extracellular matrix (ECM) pathways, as well as environmental factors such as smoking, hypertension, cardiovascular disease, diabetes mellitus, age-related changes, and metabolic stress (Fleckenstein et al. 2021).

The protective role of clusterin in AMD and its potential therapeutic implications have been highlighted in recent research. The secretion of clusterin was observed to increase in response to pan-HDAC inhibitors in ARPE-19 cells, suggesting a potential therapeutic effect of HDAC inhibitors in AMD (Yoshida et al. 1995; Suuronen et al. 2007). However, within the retinas of dry AMD patients, HDAC1 and HDAC2 may exert a protective function by directly binding to the CCL26 promoter region and epigenetically repressing gene expression. Genetic knockout or pharmacological inhibitor treatment leads to an increase in CCL26 expression. Consequently, the use of pan-HDAC inhibitors or the targeting of HDAC1 and HDAC2 may have a negative effect on the pathogenesis of dry AMD (Dubey et al. 2022).

Wet AMD Neovascularization of the choroid is a critical feature of wet AMD. During this process, VEGF plays a crucial role and serves as a clinical biomarker and therapeutic target

of wet AMD. Sirt1 could play a protective role in wet AMD conditions. RPE cells from AMD donors exhibit decreased Sirt1 expression (Zhang et al. 2020). The oral nutritional supplement of resveratrol produces long-term beneficial effects on wet AMD patients (Richer et al. 2014; Zhang et al. 2014).

The laser-induced choroidal neovascularization model is very well-known and best represents angiogenesis in wet AMD. When G570 (indoline-based hydroxamate), an HDAC6-HSP90 inhibitor was administered in this model, its therapeutic effect was equivalent to that of the FDA-approved aflibercept, with a comparable decrease in the neovascular area (Hsu et al. 2021). During angiogenesis in wet AMD, the RPE layer is continuously stimulated by VEGF, which weakens the tight junctions. HDAC6 is involved in the EMT pathway and increased in the cytosol via TGF-β1 stimulation. HDAC6 acts as an epigenetic repressor to tight junction proteins by entering the nucleus and deacetylating lysine 5 of histone H2B (Shan et al. 2008; Deskin et al. 2016; Gu et al. 2016; Mobley et al. 2017). Those signaling pathways might be involved in the pathogenesis of wet AMD. Collectively, the evidence suggests that Sirt1 activators and HDAC6 inhibitors hold therapeutic potential against wet AMD.

Dysregulation of HDACs in glaucoma

Globally, glaucoma is the most common cause of irreversible blindness (Tham et al. 2014). It encompasses a group of conditions with heterogeneous causes, resulting in cupping of the optic nerve head, loss of retinal ganglion cells (RGCs), and ECM remodeling (Jonas et al. 2017). Glaucoma is divided into open-angle and angle-closure glaucoma depending on the shape of the anterior chamber angle (King et al. 2013; Weinreb et al. 2016). The most common form of glaucoma is primary open-angle glaucoma (POAG), which is caused by increased pressure in the eye due to resistance in the trabecular meshwork (Bellezza et al. 2003; Weinreb and Khaw 2004). In contrast, primary angle-closure glaucoma (PACG) is caused by physical blockage of the drainage pathway of the front chamber by eye tissue, usually the iris (King et al. 2013). The risk factors for POAG include aging (Rudnicka et al. 2006; Kim et al. 2012a, 2016), elevated intraocular pressure (IOP) (Kass et al. 2002; Musch et al. 2009; Kim et al. 2016), sub-Saharan African ethnicity (Rudnicka et al. 2006; Leske et al. 2007), and severe myopia (Qiu et al. 2013). Aging, hyperopia, and East Asian ethnicity are the main risk factors for PACG (Congdon et al. 1997; Dandona et al. 2000; Moghimi et al. 2015). The pathophysiology of glaucoma is usually associated with an increase in IOP (Weinreb et al. 2014). The lamina cribrosa, through which the optic nerve fibers cross the sclera, represents the most vulnerable point in the pressurized eye wall (Quigley et al. 1981). The mechanical stress and strain resulting from increased IOP can lead to the compression, distortion, and alteration of the lamina cribrosa, ultimately causing mechanical damage to the axons and disrupting their transport (Burgoyne et al. 2005). Prevention and slowing disease progression are the main goals of glaucoma treatment. To target IOP, several different classes of topical pressure-lowering medications are available. In general, prostaglandin analogs are the first-line medical therapy (Weinreb et al. 2014).

Previous studies have provided evidence regarding the involvement of HDACs in the pathogenesis of glaucoma. A positive correlation between HDAC6 mRNA expression levels and disease progression has been reported, as evidenced by neuroretinal rim area in POAG patients (Siwak et al. 2018). In a rat model of chronic glaucoma induced by hypertonic saline injection, increased protein expression and activity of HDAC1, HDAC 2, HDAC3, and HDAC6 were observed (Zaidi et al. 2020). It is noteworthy that some patients with open-angle glaucoma exhibit normal IOP, which is referred to as normal-tension glaucoma, low-tension glaucoma, or normal pressure glaucoma (Leske 1983; Heijl 2015). Glutamate/aspartate transporter (GLAST)-deficient mice are a model of normal-tension glaucoma (Harada et al. 2007). This animal model exhibits a thin inner retinal layer and degeneration of RGCs, indicating typical glaucoma lesions (Kimura et al. 2015; Sano et al. 2019). When valproic acid, an HDAC inhibitor, was administered to GLAST KO mice, the number of cells in the RGC layer and the thickness of the inner retinal layer were increased (Kimura et al. 2015).

Some reports have suggested a relationship between glaucoma and epigenetic changes in the trabecular meshwork or Schlemm's canal (Matsuda et al. 2015; McDonnell et al. 2016; Chansangpetch et al. 2018; Cai et al. 2020). This epigenetic regulation may be linked to the function of HDACs. In a rabbit model of increased IOP caused by TGF-β2 injection, the administration of SAHA (suberoylanilide hydroxamic acid), a pan-HDAC inhibitor, improved the increase in IOP. Additionally, treatment of SAHA suppressed the elevation of transepithelial electrical resistance values, ECM protein expression, and cytoskeletal protein expression at trabecular meshwork and Schlemm's canal cells induced by TGF-β2. It has been shown that the effect of SAHA was due to the regulation of the non-SMAD pathway of TGF-β signaling (Fujimoto et al. 2021).

Dysregulation of HDACs in retinopathy of prematurity

ROP is an ocular disorder that predominantly afflicts preterm neonates. The disorder affects the vascular and neural tissue layers of the retina, which are responsible for photodetection and neural signal transmission to the visual centers in the brain. ROP manifests most frequently in neonates born

preterm, specifically those born before 31 weeks of gestation or with a birth weight of less than 1250 g. This susceptibility arises due to the incompleteness of the retinal vascularization process at birth, necessitating further maturation and development (Zin and Gole 2013; Alajbegovic-Halimic et al. 2015). Infants who require oxygen therapy because of respiratory distress syndrome or other conditions are at an increased risk of developing ROP. High oxygen levels can damage developing blood vessels in the retina, leading to abnormal growth (Pierce et al. 1996; Hartnett and Lane 2013). Infants with other medical conditions, such as anemia, sepsis, and apnea, are also at a higher risk of developing ROP (Lundgren et al. 2018; Goldstein et al. 2019). It is noteworthy that not all premature infants develop ROP, and that the severity of this condition can vary widely among those who do. Therefore, early detection and treatment of ROP are important to prevent vision loss or blindness.

The traditional approach for treating ROP involves photocoagulation, which uses laser beams to seal and close abnormal blood vessels in the underdeveloped retina. However, this method may present challenges such as poor visualization of the blood vessels and scarce availability in resource-limited settings. Conversely, anti-VEGF therapy raises uncertainties regarding optimal dosages, potential ocular complications, and systemic adverse reactions in the cardiovascular system and neurodevelopment, which are important considerations in ROP treatment decisions. These challenges underscore the need for further development of novel drug therapies in the field (Valikodath et al. 2021).

Dysregulation of HDACs in retinitis pigmentosa

Retinitis pigmentosa is a group of genetically inherited disorders that primarily affect the retina, leading to gradual vision loss and blindness (Hartong et al. 2006). Mutations in genes that are essential for the structure and function of retinal cells might interfere with the normal development, maintenance, and survival of retinal cells, leading to their progressive degeneration over time (Hamel 2006). The fundamental treatment consists of conservative treatment, and in a few particular cases, gene therapy or stem cell treatment (Wu et al. 2023). For example, noretigene neparvovev-ryzl (Luxturna®) has been FDA-approved for RPE65 gene-mutated patients, a specific retinitis pigmentosa type (Maguire et al. 2019). The *phosphodiesterase 6b* (*Pde6b*) gene mutation models, such as rd1 and rd10 mice, are one of the most well-known animal models. Those mice show progressive photoreceptor degeneration over time (Bowes et al. 1990; Chang et al. 2002, 2007). Rd1 mice show increased HDAC activity and hypoacetylation of lysine in the outer nuclear layer of the retina (Sancho-Pelluz et al. 2010). These findings suggest HDACs dysregulation during retinal degeneration. Intravitreal injection of trichostatin A as a pan-HDAC inhibitor or tubastatin A as an HDAC6 inhibitor increased cone cell survival in animal models (Sundaramurthi et al. 2020; Samardzija et al. 2021). Additionally, intraperitoneal injection of romidepsin, an HDAC1 and HDAC2 inhibitor, into rd10 mice shows efficacy against retinitis pigmentosa (Popova et al. 2021). Clinical studies using valproic acid suggested beneficial effects for patients (Clemson et al. 2011; Kumar et al. 2014). These results indicate that the HDACs involved in retinitis pigmentosa pathogenesis and its inhibition delay disease progression. Further research is needed to determine whether HDAC regulates gene function itself or if it regulates disease progression. Additionally, specific profiling of HDAC dysregulation in each type of retinitis pigmentosa is required.

Dysregulation of HDACs in retinoblastoma

Retinoblastoma is a rare and aggressive form of cancer that primarily affects the retina. It is the most common primary malignant intraocular cancer among the pediatric population and is almost exclusively found in young children. The condition is mainly caused by mutations in the RB1 gene, which encodes the retinoblastoma protein (pRB) (Dimaras et al. 2012). The pRB protein plays a crucial role in regulating the cell cycle from the G1 to the S phase and preventing uncontrolled cell division. Mutations in the RB1 gene lead to the loss of normal pRB protein function, resulting in uncontrolled growth and proliferation of retinal cells, ultimately leading to retinoblastoma (Henley and Dick 2012; Zhou et al. 2022). Aberrant histone deacetylation can contribute to retinoblastoma formation (McEvoy and Dyer 2015). pRB inhibits the cyclin E gene by interacting with E2F transcription factors and HDAC1. Trichostatin A treatment suppresses the cell cycle by inhibiting HDAC1 (Brehm et al. 1998; Magnaghi-Jaulin et al. 1998). Moreover, trichostatin A treatment induces apoptosis in human retinoblastoma cells (Dalgard et al. 2008). Pan-HDAC inhibitors treatment reduces the promoter activity of c-myc as a proto-oncogene in a retinoblastoma cell line (Yu et al. 2020). High expression of HDAC9 correlates with a poor prognosis, while its downregulation reduces cell proliferation via cell cycle arrest in retinoblastoma cells (Zhang et al. 2016b). These findings suggested targeting HDACs as a potential therapeutic strategy for managing retinoblastoma.

Dysregulation of HDACs in optic neuropathy

Optic neuropathy refers to damage or dysfunction of the optic nerve, which can lead to vision problems. There are various causes of optic neuropathy in ocular disease, and the pathogenesis is associated with HDACs (Schmitt et al. 2016; Pan et al. 2023).

Ischemic optic neuropathy occurs when insufficient blood flow to the optic nerve leads to tissue damage (Chiquet et al. 2022). Non-arteritic anterior ischemic optic neuropathy, which occurs after glaucoma, is the most common form of optic neuropathy and typically occurs at ages 50 and older (Dworak and Nichols 2014). The optic nerve becomes ischemic, resulting in swelling and damage to the nerve fibers, which can lead to vision loss (Fu et al. 2021). HDACs are deeply involved in the apoptosis process of RGCs. The optic nerve crush mice model shows an increased level of HDAC2 and HDAC3 protein expression and activity in the RGC layer. Furthermore, administration of trichostatin A, pan-HDAC inhibitors, or apicidin, an HDAC 2 and 3 inhibitor, ameliorates disease phenotypes after optic nerve crush (Crosson et al. 2010; Pelzel et al. 2010). Additionally, genetic evidence supports that cell survival and electroretinography of GCL, recover to the normal level in the $HDAC2^{+/-}$ mice in the ischemic neuropathy injury model (Fan et al. 2013). One study suggests that the activation mechanism of HDAC3 within the neuronal system is through phosphorylation by GSK3β, resulting in a cytotoxic effect on neurons (Bardai and D'Mello 2011). The RGC-specific knock-out of HDAC1 and HDAC2 promotes RGC survival in the optic nerve axotomy injury model (Lebrun-Julien and Suter 2015).

Optic neuritis is often associated with autoimmune diseases such as multiple sclerosis (Kale 2016). In this condition, the immune system attacks the myelin sheath surrounding the optic nerve. Demyelination disrupts the normal transmission of nerve signals, causing inflammation and damage to the optic nerve leading to vision problems (Ma et al. 2022). Valproic acid administration in the induced experimental autoimmune encephalomyelitis mouse model led to a reduction in the Iba1-positive area and demyelination, thereby ameliorating the lesion. These results suggest that HDACs were involved in optical neuritis lesions (Azuchi et al. 2017). Based on these findings, targeting HDACs can be a treatment option for patients with optic neuropathy.

Role of TGF-β signaling in ocular pathologies

TGF-β signaling plays a pathological role in ocular disease. It is initiated by the phosphorylation of Smad2 and Smad3. These proteins form complexes with Smad4 and translocate to the nucleus to transduce downstream signals (Akhurst and Hata 2012). This signaling pathway promotes the excessive production of ECM components like collagen and fibronectin, resulting in the formation of fibrotic tissue. These changes can lead to tissue contraction, disruption of retinal structure, and impaired visual function (Hachana and Larrivee 2022). For instance, TGF-β signaling enhances outflow resistance via ECM remodeling of the trabecular meshwork in glaucoma (Prendes et al. 2013; Wang et al. 2017; Kasetti et al. 2018). Additionally, it induces epithelial-to-mesenchymal transition (EMT), causing the breakdown of the cell junctions and transition to mesenchymal status, which contributes to the disruption of the blood-retinal barrier (Chen et al. 2017; Zou et al. 2020). Furthermore, it could stimulate the release of VEGF and lead to retinal edema/hemorrhage through pro-angiogenic Smad1/5/8 signaling mediated activation of leucine-rich α-2-glycoprotein 1 in endothelial cells (Wang et al. 2013). This section focuses on the crosstalk between TGF-β signaling and HDACs.

HDACs deacetylate SMAD complexes

Smad2/3

Smad2/3 undergoes acetylation in the nucleus, which activates its transcriptional activity (Inoue et al. 2007; Tu and Luo 2007). Sirt1 reduces TGF-β1 signaling-mediated transcriptional activity by deacetylating Smad3. The overexpression of Sirt1 and its activation by resveratrol reduces Smad3 acetylation and attenuates ECM protein expression. Conversely, the knockdown of Sirt1 leads to the accumulation of acetylated Smad3 and enhances TGF-β signaling-mediated transcriptional activity (Huang et al. 2014). Sirt6 reduces Smad2/3 transcriptional activity through deacetylation of K54 and K378, respectively (Maity et al. 2020; Zhang et al. 2021). HDAC6 also regulates Smad3 acetylation. The inhibition of HDAC6 via tubastatin A suppresses TGF-β signaling by promoting Smad3 acetylation at the K19 site in the cytoplasm, thereby preventing Smad2/3 phosphorylation and nuclear translocation (Osseni et al. 2022).

Smad4

Smad4 is deacetylated by Sirt1 and Sirt7, increasing its ability to regulate gene expression (Simic et al. 2013; Chen et al. 2014; Tang et al. 2017; Li et al. 2018). While the precise site of the interaction between Sirt1 and Smad4 has not yet been fully elucidated, Sirt1 has been shown to inhibit TGF-β signaling by deacetylating Smad4 under certain circumstances (Simic et al. 2013; Chen et al. 2014; Li et al. 2018). Sirt7 deacetylates Smad4 at the K428 residue and blocks TGF-β signaling by deacetylating Smad4, which results in its destabilization (Tang et al. 2017).

Smad7

TGF-β signaling upregulates Smad7, which primarily acts as a negative regulator (Nakao et al. 1997). However, Smad7 also exhibits positive regulatory effects on gene expression

(Thakur et al. 2020) and is implicated in TGF-β-induced apoptosis (Lallemand et al. 2001; Okado et al. 2002; Kume et al. 2007). Smad7 is acetylated at lysine residues 64 and 70. The balance between acetylation and ubiquitination controls its stability. Smurf1 mediates the degradation of deacetylated Smad7 via the ubiquitin-proteasome system (Grönroos et al. 2002). HDAC1, HDAC3, HDAC6, and Sirt1 could deacetylate Smad7 and enhance its degradation (Fig. 2) (Simonsson et al. 2005; Kume et al. 2007; Sedda et al. 2018).

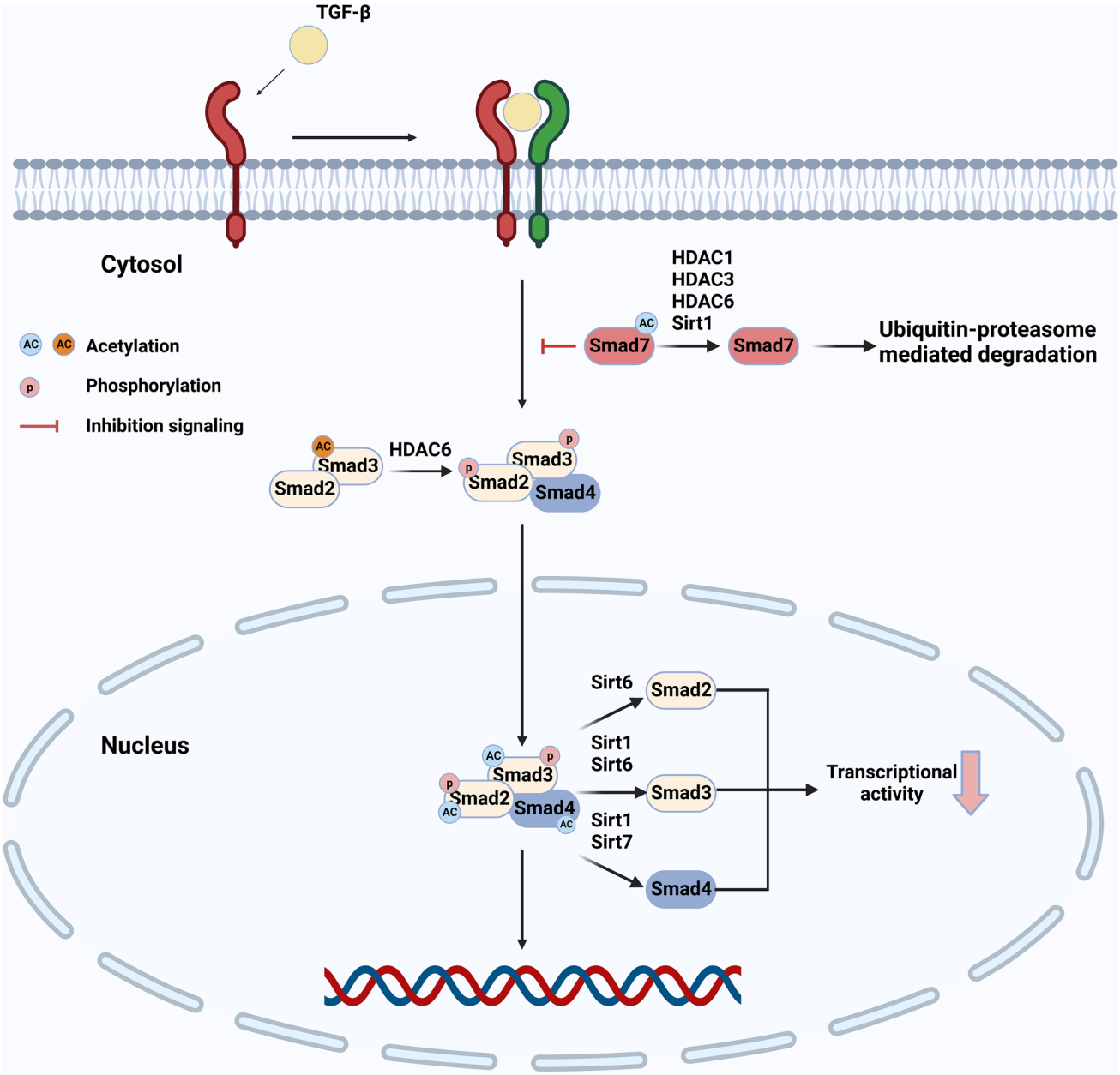

Fig. 2 The regulatory mechanism of TGF-β signaling by HDACs through the deacetylation of Smad proteins. The TGF-β signaling cascade is initiated by the phosphorylation of Smad2 and Smad3, which form complexes with Smad4 and translocate to the nucleus, where they activate downstream signaling pathways. This schematic diagram illustrates how HDACs modulate TGF-β signaling at each cascade step by deacetylating Smad proteins. Figures were created with Biorender.com

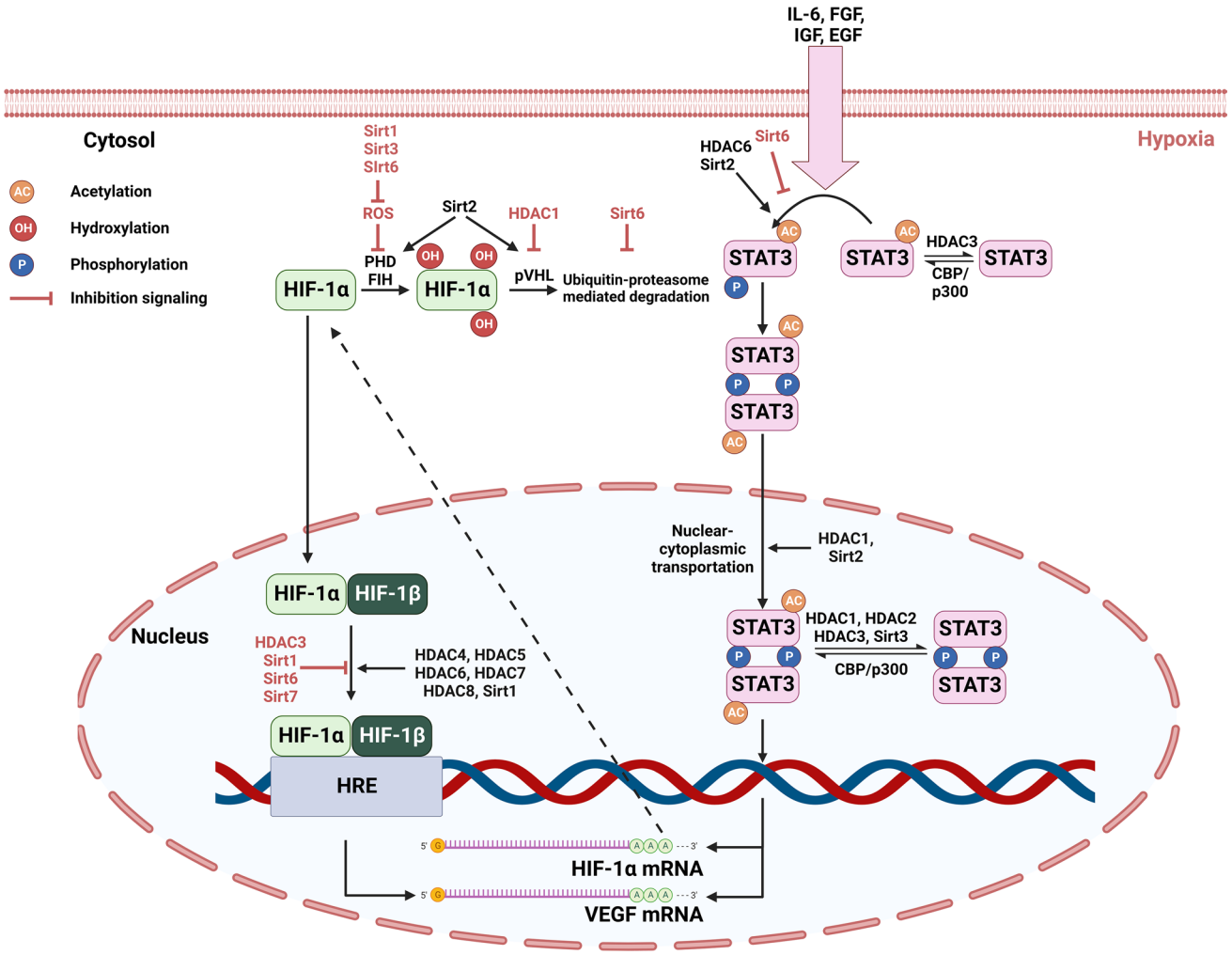

Fig. 3 HDACs-mediated regulation of VEGF expression. HIF-1α is a well-known transcription factor for VEGF, which stabilizes under hypoxic conditions due to ROS-mediated inhibition of HIF-1α hydroxylation and ubiquitin-proteasome-mediated degradation. HIF-1α translocates into the nucleus and forms a dimer with HIF-1β, leading to its role as a transcription factor for VEGF. Additionally, STAT3 acts as a transcription factor for both VEGF and HIF-1α. We present the role of HDACs in promoting or inhibiting VEGF expression in each signaling step. Figures were created with Biorender.com

Effect of VEGF signaling in the pathology of ocular diseases

VEGF plays a critical role in angiogenesis. The growth of blood vessels is vital for providing nutrients to tissues and organs. However, uncontrolled angiogenesis can lead to disease, including tumors and intraocular vascular disorders such as DR, AMD, and ROP. Targeting VEGF has prevented blindness in millions of patients with eye diseases, as well as increased survival of patients with various types of cancer (Adamis and Shima 2005; Ferrara 2016). VEGF was significantly increased in the aqueous humor in neovascular glaucoma, wet-AMD, and PDR patients (Lim et al. 2009; Chalam et al. 2014; Hsu et al. 2016). Abnormal or excessive VEGF production can lead to the growth of fragile, leaky blood vessels within the retina (Jo et al. 2016). This neovascularization disrupts the typical retina architecture and can lead to vision impairment or even blindness. In the endothelial cells of the retina, VEGF-A binds to VEGF receptor 2, inducing phosphorylation

Table 1 HDACs regulate the post-translational modification of transcription factors for VEGF gene expression

Classification			Biological functions	References
Zinc dependent HDACs	Class I	HDAC1/2	HDAC1 stabilizes HIF-1α by forming a complex with metastasis-associated protein 1. In addition, STAT3 acetylation at Lys685 via p300 is responsible for the deacetylation of HDAC1 and HDAC2	Yuan et al.(2005), Yoo et al. (2006), Yeh et al. (2013)
		HDAC3	HDAC3 is essential to phosphorylation at the Y705 of STAT3 in liver cancer cells	Xiao et al. (2006), Zeng et al. (2006), Lu et al. (2018)
		HDAC8	HDAC8 binds directly to HIF-1α and deacetylates it, increasing transcriptional activity such as hexokinase2 and glucose transporter1	Kim et al. (2023)
	Class IIa	HDAC4	HDAC4 deacetylates lysine residues (Lys10, 11, 12, 19, and 21) in HIF-1α N-terminal to increase its transcriptional activity	Geng et al.(2011)
		HDAC5	HDAC5 regulates HIF-1α stability and transactivation by controlling the acetylation level of Hsp70	Chen et al.(2015)
		HDAC7	HDAC7 and HIF-1α combine to be translocated to the nucleus and increase the transcriptional activity of HIF-1α	Kato et al. (2004)
	Class IIb	HDAC6	HDAC6 increases HIF-1α stability and transcriptional activity	Qian et al. (2006)
NAD^+ dependent sirtuins	Class III	Sirt1	Sirt1 inhibits transcriptional activity by deacetylating HIF-1α at Lys674 and STAT3 at Lys685, 679, 707, and 709	Lim et al. (2010), Sestito et al. (2011), Park et al. (2014)
		Sirt2	Sirt2 causes ubiquitination of HIF-1α by deacetylating HIF-1α at the Lys709. In addition, Sirt2 increases VEGFA secretion by phosphorylation STAT3 at Y705	Seo et al. (2015), Hu et al. (2018)
		Sirt3	Sirt3 does not directly bind to HIF-1α but destabilizes it. In addition, Sirt3 regulates transcriptional activity by deacetylating STAT3	Bell et al. (2011), Finley et al. (2011), Guo et al. (2017)
		Sirt6	Sirt6 acts as a co-repressor of HIF-1α and deacetylating the histone H3K9 of the HIF-1α target gene. In addition, Sirt6 inhibits tumor growth by inhibiting JAK2/STAT3 phosphorylation	Zhong et al. (2010), Feng et al. (2016), Zhou et al. (2017)

of VE-cadherin at Y685 (Smith et al. 2020), and eNOS at S1177. This results in elevated NO production and increased vascular permeability (Park et al. 2019). VEGF signaling is also involved in producing pro-inflammatory cytokines (Hachana et al. 2020).

HDACs regulate the VEGF-mediated angiogenesis process. HDAC3 is a pivotal mediator in VEGF-triggered endothelial cell differentiation and angiogenesis, and the VEGF receptor 2-PI3K-Akt signaling cascade regulates its activity. Upon activation by this cascade, HDAC3 deacetylates p53, culminating in the activation of p21 (Xiao et al. 2006; Zeng et al. 2006). Class II HDACs such as HDAC5, HDAC6, and HDAC7 have angiogenic functions in endothelial cells (Wang et al. 2008; Urbich et al. 2009; Kaluza et al. 2011; Zecchin et al. 2014). VEGFR-2 signaling activates PDK-1, which phosphorylates and activates HDAC5 at the sites Ser259 and Ser498, as well as HDAC7 at the sites of Ser178, Ser344, and Ser479. Activated HDAC5 and HDAC7 are involved in angiogenesis (Ha et al. 2008; Wang et al. 2008). Moreover, HDAC5 and HDAC6 directly bind to VEGFR-2 and regulate its acetylation level and function (Zecchin et al. 2014). Sirt1

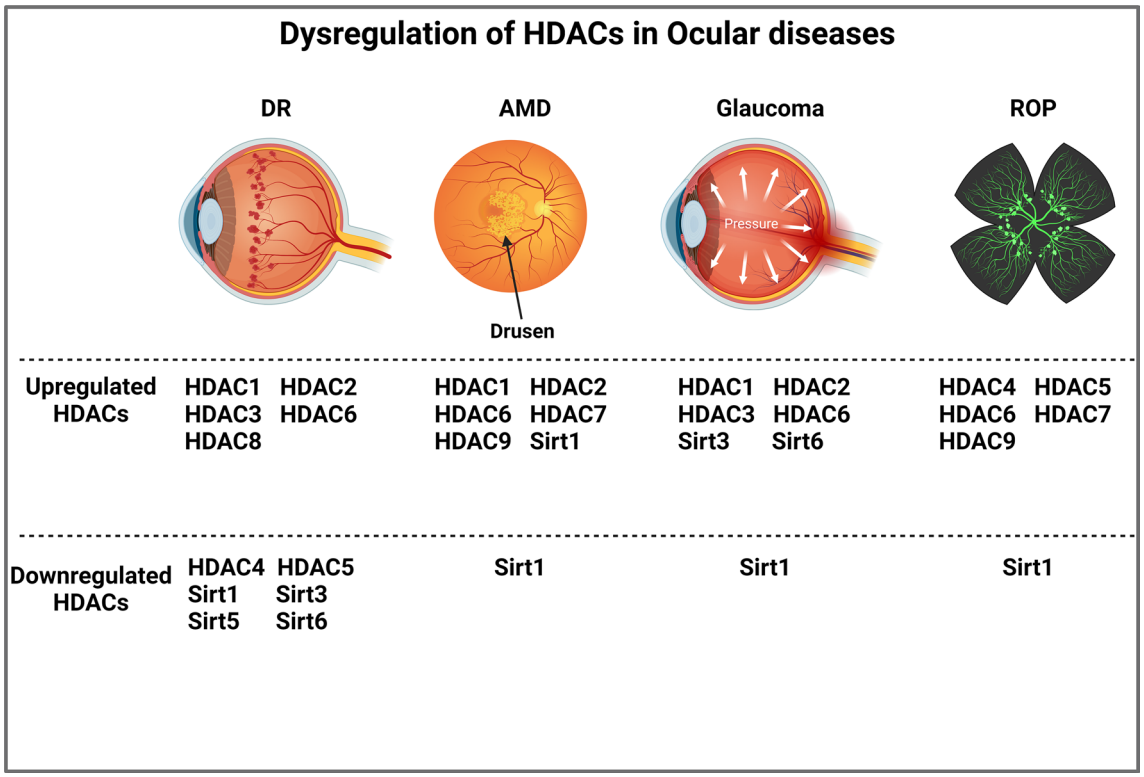

Fig. 4 Dysregulation of HDACs in ocular diseases. A schematic demonstration depicts the dysregulation of HDACs in ocular diseases such as DR, AMD, Glaucoma, and ROP. These diseases are complicated and involve forming new blood vessels, neurodegeneration, and/or inflammation inside the eye. We presented upregulated and downregulated HDACs in each disease condition. Reference to DR: (Zhong and Kowluru 2010; Kowluru et al. 2014; Silberman et al. 2014; Cai et al. 2017; Mishra and Kowluru 2017; Peshti et al. 2017; Zorrilla-Zubilete et al. 2018; Abouhish et al. 2020; Fu et al. 2020; Hammer et al. 2021; Che et al. 2022). Reference to AMD: (Kaluza et al. 2013; Maloney et al. 2013; Ishida et al. 2017; Dahbash et al. 2019; Xiao et al. 2020; Hamid et al. 2021; Zhao et al. 2022). Reference to glaucoma: (Yang et al. 2014; Zhang et al. 2016a; Siwak et al. 2018; Yaman et al. 2020; Zaidi et al. 2020). Reference to ROP: (Wang et al. 2008; Chen et al. 2013; Ran et al. 2020, 2022; Bahl and Seto 2021). Figures were created with Biorender.com

also regulates VEGF receptor expression. It enhances the mRNA expression of VEGFR-1 and VEGFR-2. By contrast, Sirt1 inhibition decreases mRNA expression (Maizel et al. 2014). Nicotinamide phosphoribosyl transferase leads to the Sirt1-dependent enhancement of Notch-1 intracellular domain deacetylation, which upregulates VEGFR-2 and VEGFR-3 (Wang et al. 2014). HDACs play a role in regulating VEGF expression under hypoxic conditions. HDACs are involved in the post-translational modification, protein stability, and nuclear-cytoplasmic transport of VEGF signaling pathway proteins, impacting angiogenesis (Fig. 3; Table 1). These findings emphasize the significance of HDACs in modulating VEGF signaling and its implications in angiogenesis and ocular diseases.

Conclusions

In conclusion, the present review provides a comprehensive analysis of the involvement of HDACs in the pathogenesis of various ocular diseases, including DR, AMD, glaucoma, and ROP (Fig. 4), as well as retinitis pigmentosa, retinoblastoma, and optic neuropathy. The limited availability of effective treatments for these complex disorders necessitates the exploration of novel therapeutic strategies. The potential of HDAC inhibitors in this context warrants further investigation, as they have shown promising neuroprotective and neuroactive properties in various neurological and ocular diseases.

In addition, this review extends beyond the field of ophthalmology. It examines the relationship between HDACs and critical regulators of fibrosis and angiogenesis, such as TGF-β and VEGF, offering valuable insights into the potential targets of HDACs under a broader range of conditions. The significance of HDACs in the development of retinal diseases, which share common features with cancer and inflammatory conditions, highlights the need for further research in this area. Given the projected increase in the incidence of retinal diseases in the coming years, it is crucial to identify effective treatments. Therefore, the potential of HDAC inhibitors as a novel therapeutic strategy for these diseases should be thoroughly investigated, and clinical trials are required to establish their efficacy and safety.

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Declarations

Conflict of interest Jae Hyun Jun is an employee of Chong Kun Dang Pharmaceutical Co. The other authors have no conflict of interest.

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