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The role of HIF-1α in neovascular ophthalmologic diseases – literature review

Monika Modrzejewska[1, A] ✉, Oliwia Zdanowska[2, B]

[1] Pomeranian Medical University in Szczecin, Second Chair and Department of Ophthalmology, Powstańców Wlkp. 72, 70-111 Szczecin, Poland
[2] Pomeranian Medical University in Szczecin, 2nd Department of Ophthalmology, Powstańców Wlkp. 72, 70-111 Szczecin, Poland

[A] ORCID: 0000-0002-9221-8909; [B] ORCID: 0009-0008-5432-3653

✉ monika_modrzej@op.pl

ABSTRACT
Worldwide, across all age groups, there is a high prevalence of eye diseases with a neovascular component, which are a significant cause of vision impairment. Hypoxia-inducible factor (HIF-1) is a key regulator in the body's adaptation to hypoxic conditions and the cellular response to oxidative stress. Additionally, it plays a crucial role in erythropoiesis, angiogenesis, and mitochondrial metabolism. This multifunctional action makes it significant in the pathogenesis and progression of neovascular eye diseases. According to available literature, HIF-1 plays a key role in the progression of ocular diseases such as age-related macular degeneration, proliferative diabetic retinopathy, retinal vein occlusion, retinopathy of prematurity, neoplastic conditions (uveal melanoma, retinoblastoma), corneal neovascularization, and the neovascular form of pterygium. This literature review summarizes the latest scientific findings regarding the role of HIF-1 in neovascular eye diseases and its potential significance in the context of developing modern therapeutic strategies.
Keywords: HIF-1; neovascularization; eye diseases.

INTRODUCTION

Neovascular ocular diseases are one of the leading causes of impaired vision, even leading to complete vision loss, in developed countries [1]. The formation of new pathological blood vessels may occur in the structures of the eye, such as the retina, choroid, and cornea. Literature describes the following stimuli that contribute to the induction of the neoangiogenesis process: hypoxia, ischemia, immune or inflammatory responses, biological stress, and genetic variability [2]. Newly formed blood vessels are characterized by increased permeability, leading to the accumulation of fluid in the extracellular space and disturbances in the proper function of eye tissues. Eye diseases in which neovascularization occurs include, among others: neovascular age-related macular degeneration (nAMD), proliferative diabetic retinopathy (PDR), retinopathy of prematurity (ROP), corneal neovascularization, retinal vessel occlusion, neovascular glaucoma, ocular histoplasmosis, and pathological myopia [1, 3]. It is estimated that AMD affects nearly 200 mln people worldwide, and by 2040, this number will increase to over 288 mln [4]. Neovascular age-related macular degeneration accounts for 10–20% of all AMD cases. Diabetic retinopathy (DR) affects over 126 mln people worldwide, and the number of people with DR is expected to rise to over 190 mln by 2030 [5]. According to literature, around 7–10% of patients with diabetes (DM) will develop PDR [6]. Retinopathy of prematurity is the leading cause of blindness in children worldwide; in 2019 ROP was reported in over 8% of premature infants born in the USA [7], and in Europe, the prevalence varies from around 9% (in Switzerland) to over 64% (in Portugal) [8]. These data highlight the widespread nature of neovascular ocular diseases globally, regardless of age group.

Hypoxia-inducible factor (HIF-1) was discovered in 1992 and is a transcription factor that functions as an intermediary regulator of the increased expression of proangiogenic genes under hypoxic conditions. It consists of 2 subunits: HIF-1α, which is sensitive to oxygen levels, and HIF-1β, which is constitutively expressed [9]. Hypoxia-inducible factor plays a stabilizing role for the structure of HIF-1α [10]. This heterodimeric complex controls oxygen homeostasis in the cell, mitochondrial metabolism, energy metabolism, cell differentiation, inflammation modulation, immune modulation, and angiogenesis [11]. The latter function will be discussed in more detail in this article in the context of neovascular ocular diseases. The authors of this review have analyzed the latest literature from the last 5 years (2020–2025) along with cited references regarding the role of HIF-1α in neovascular ocular diseases.

DISCUSSION

Neovascular age-related macular degeneration

In the course of nAMD, there is the development of choroidal neovascularization (CNV), where newly formed pathological blood vessels may lead to the formation of retinal edema, most commonly macular edema, hemorrhagic bleeds, and ultimately irreversible retinal atrophy [12]. Neovascular age-related macular degeneration is not classified as a typical ischemic retinal disease. However, there is evidence supporting the role of HIF-1 in the development of CNV in nAMD, through the stimulation of vascular endothelial growth factor (VEGF) gene transcription [13]. Sheridan et al. reported increased HIF expression in

surgically prepared CNV specimens obtained from patients diagnosed with nAMD [14]. To date, literature has not described a specific cause for the accumulation of HIF-1α in the ocular tissues of AMD patients. Researchers Babapoor-Farrokhran et al. developed a hypothesis pointing to ischemic pathogenesis of this phenomenon, based on hypoxia in the retinal pigment epithelium (RPE) in eyes with AMD. This process is multifactorial, occurring both through the impaired function and fragility of blood vessels in older patients, which fail to deliver sufficient oxygen to the RPE, as well as the accumulation of drusenoid material, which creates a mechanical barrier hindering oxygen diffusion from capillaries to the retina [15]. The hypothesis was supported by the discovery of El Matri et al., who demonstrated that a thin choroid in patients with high myopia predisposes them to CNV development. Babapoor-Farrokhran et al. [15] also considered another mechanism for HIF-1's influence on nAMD pathogenesis, based on the role of HIF-1 in the eye cells' response to oxidative stress, its accumulation in tissues, and the stimulation of angiogenic factor expression, leading to the development of CNV. The above literature suggests that stabilizing HIF-1 seems to be a promising therapeutic approach for nAMD. Up until the year 2000, thermal laser photocoagulation targeting neovascular changes was considered the standard method for treating nAMD. Another approved therapeutic method became photodynamic therapy (PDT), which requires intravenous administration of verteporfin (a photosensitizing dye) that accumulates within the CNV area. The limitation of laser therapy is the long treatment time, the need for analgesia, and the risk of adverse effects such as retinal damage, visual field restriction, or development of high myopia. Additionally, PDT carries the risk of hypersensitivity reactions and other systemic adverse effects [12]. A revolution in nAMD therapy came with the possibility of intravitreal anti-VEGF injections. However, this type of treatment requires repeated injections and regular monitoring, and it is also associated with the risk of side effects. The most frequently described local side effects in the literature include subconjunctival hemorrhage, vitreous hemorrhage, increased intraocular pressure, retinal detachment, endophthalmitis, cataract, as well as less common systemic effects such as dysfunction of parenchymal organs (liver and kidneys), respiratory failure, or thromboembolic complications [16, 17]. The above literature suggests a real need for the development of new, effective therapeutic methods for AMD. Given the significant role of HIF-1 in the pathogenesis of this disease, further research on utilizing this knowledge in the design of new nAMD therapies seems justified.

Proliferative diabetic retinopathy

Numerous reports in the literature associate the role of the HIF-1 factor with neovascularization and neurodegeneration of the retina in the course of DR [18, 19, 20, 21, 22]. In the course of PDR, pathological retinal blood vessels are synthesized, often accompanied by hemorrhages into the vitreous body or subretinal space. Abnormal vessels can also affect other ocular tissues, such as the iris or the filtration angle, which consequently leads to the development of neovascular glaucoma [2]. Current treatment is based on intravitreal injections of anti-VEGF and laser photocoagulation, with surgical intervention being necessary in some cases. Several mechanisms contribute to retinal hypoxia in DM, including oxidative stress, pericyte loss, endothelial cell damage, microaneurysms, increased white blood cell levels, and advanced glycation end products. All of these processes contribute to capillary damage and ischemia of the oxygen-sensitive retina, even in the early stages of DR [23]. Under reduced oxygen levels, HIF-1α is activated, forming a transcription complex with the HIF-1β subunit and increasing the expression of angiogenic factors regulated by HIF, which play an essential role in the development of diabetic macular edema (DME) [24] and PDR [25]. The literature contains reports on the correlation between the level of HIF-1α and the stage of DR [26]. Bilgin et al. in their study described the correlation between survivin expression and the stage of DR. Survivin, dependent on the activation of the HIF-1α pathway, contributes to the progression of DR [26]. Patients with DM are particularly susceptible to incidental episodes of hypoglycemia, which may result from improper treatment (especially in the early stages of the disease), sports activity, alcohol consumption, inadequate carbohydrate intake, increased insulin absorption in high environmental temperatures, or intensified insulin action during early pregnancy or rapid weight loss. Among many DM patients, awareness of hypoglycemia is lowered, which significantly hinders early detection and the ability to respond quickly [27]. Reduced blood glucose levels lead to the replacement of the glycolysis process with oxidative phosphorylation, resulting in hypoxia and, consequently, increased activation and accumulation of HIF-1α, which leads to increased expression of the GLUT1 glucose transporter in Müller cells of the retina, and lactate via lactate dehydrogenase-A and pyruvate dehydrogenase kinase 1. The above reports indicate the key protective role of HIF-1α in Müller cells under hypoglycemic conditions. However, researchers Guo et al., in their publication, described the negative side of this phenomenon, confirming that accumulated HIF-1α under hypoglycemic conditions also increases the expression of proangiogenic factors, which increases the risk of pathological neovascularization. The above findings highlight the importance of HIF-1 as a potential molecular target for PDR, especially in patients experiencing significant glycemic variability in DM, as well as those exposed to high glucose levels in undiagnosed or uncontrolled DM during the initial phase of treatment, when there is the highest risk of a rapid decrease in blood glucose levels [28].

Retinopathy of prematurity

A disease widely prevalent among pediatric patients born prematurely, before the 37th week of pregnancy, and a cause of severe visual disturbances. In the course of ROP, 2 stages can be distinguished: the first, which involves microvascular degeneration of the immature retina, and the second, known as the phase of fibrovascular proliferation [29]. In the immature ocular structures of premature infants, especially those exposed to hyperoxia, particularly during assisted ventilation in the first weeks of life, oxidative stress and overproduction of reactive

oxygen species occur. Consequently, there is suppression of the HIF factor and inhibition of the transcription of genes regulated by it, which are proangiogenic. The first phase involves the progressive degeneration and occlusion of retinal blood vessels, resulting in ischemia of its structures. In the second phase, as a consequence of hypoxia, there is the development of neovascularization [30, 31]. Pathological blood vessels are characterized by increased permeability and may penetrate into the vitreous cavity, leading to fibrosis and subsequently to tractional retinal detachment [32]. The underlying process involves increased expression of the HIF factor in response to hypoxia and the increased release of growth factors that stimulate the synthesis of pathological blood vessels, especially VEGF [33]. Currently used methods for treating ROP include laser therapy and anti-VEGF injections. The literature describes numerous experimental genetic studies focused on stabilizing the HIF-1 pathway and its impact on halting disease progression and counteracting neovascularization in the course of ROP. Modrzejewska et al. summarized the latest research on methods for stabilizing the HIF factor in their literature review. The algorithms proposed so far are based on inhibiting HIF, PHD, the function of non-coding RNA, APE1/Ref-1 proteins, and the impact of bone marrow cells and liver metabolism on HIF expression, as well as the role of lowered IOP in the development of neovascular diseases [33].

Retinal vein occlusion

Retinal vein occlusion (RVO) is the consequence of stenosis, thrombosis, or impaired vasodilation of the retinal venous vessels. RVO is the second most common vascular retinal disease. In 2015, the global prevalence of RVO in individuals aged 30–89 years was 0.77%, corresponding to approx. 28 mln patients worldwide. The main risk factors include: advanced age, hypertension, atherosclerosis, DM, smoking, hypercholesterolemia, elevated creatinine levels, hyperhomocysteinemia, the presence of anticardiolipin antibodies, kidney diseases, and a positive history of previous myocardial infarction, stroke, or embolic-thrombotic disease in another location [34]. Ocular risk factors include glaucoma or elevated intraocular pressure, which can hinder venous outflow [35]. The most serious complications of RVO mentioned in the literature are macular edema and neovascularization of both the anterior and posterior segments of the eye. Hayreh and Zimmerman in their study determined the 6-month probability of neovascularization development in central retinal vein occlusion (CRVO), which was 49% in the iris, 37% in the angle of the anterior chamber, 6% in the optic disc area, and 9% for the retina [36]. The development of these complications is contributed by limited vascular perfusion, inflammation of adjacent structures, and increasing tissue hypoxia. All these factors stimulate the expression of HIF-1α, which, as the main regulator of oxygen homeostasis, responds by increasing the transcription of proangiogenic factors, promoting the synthesis of new blood vessels. The hypothesis describing this pathomechanism is confirmed by literature reports. Hu et al. increased mRNA levels of HIF-1α were noted in the aqueous humor of patients with CRVO complicated by macular edema, which was consistent with an earlier study by Yan et al. [37]. Qin et al. described the interaction of baicalin with the HIF-1α/VEGFA pathway, causing its suppression by stimulating the anti-inflammatory and antioxidant activity of ARPE-19 cells. It was demonstrated in a model of branch retinal vein occlusion (BRVO) in rats that inhibition of HIF-1α leads to regression of damage and regeneration of the retinal ganglion cell layer [38]. No safe and effective method for treating and preventing vascular occlusion in RVO has been developed so far. Current therapies mainly focus on treating or preventing complications. Therapies include anti-VEGF injections, steroids, and laser therapy [39]. These reports show that there is a real need for further research on the development of new molecular targets and therapeutic methods for RVO.

NEOVASCULARIZATION IN NEOPLASTIC DISEASES

Uveal melanoma

Uveal melanoma (UM) is the most common primary intraocular malignant tumor in adults and can develop in all parts of the uveal tract (iris, ciliary body, and choroid). Its incidence varies depending on geographical location, with the highest number of cases reported in the populations of Northern and Western Europe and Oceania (>8 cases per mln person-years) [40]. Uveal melanoma has a high tendency for rapid growth and hematogenous spread, with more than 50% of patients developing metastases. Distant metastases most commonly localize in the liver. Despite significant advances in ophthalmic oncology, UM continues to be associated with high mortality [41]. The currently used local therapies, such as radiotherapy and laser therapy, are associated with a high risk of complications, ranging from visual field loss to complete vision loss. These findings highlight the urgent need for the development of new, safe therapeutic methods aimed at halting tumor spread.

Neovascularization in UM is a process that promotes tumor growth and progression, as well as invasion and metastasis development. This process is regulated by the release of proangiogenic factors from tumor cells, infiltrating inflammatory cells, and the extracellular matrix [42]. Numerous scientific publications confirm this, reporting increased levels of proangiogenic factors in patients with UM [43, 44, 45, 46]. Vascular endothelial growth factor expression can be stimulated by the expression of several oncogenes, such as EGFR, ras, erbB2/human epidermal growth factor receptor 2 (HER2), src, as well as hypoxia [47].

The literature describes significant limitations of targeted antiangiogenic therapy as a primary treatment for skin melanoma. Clinical studies on the use of anti-VEGF treatment in melanoma therapy show effects contrary to expected outcomes, based on the stimulation of angiogenesis regulators in cancer cells, which may additionally stimulate carcinogenesis and the spread of the cancer process [48, 49, 50, 51]. The major regulatory function of the secretion of angiogenic factors such as VEGF or ANGPTL4 is carried out by HIF-1. Hu et al. concluded that future therapeutic options aimed at inhibiting angiogenesis in UM should target multiple angiogenic factors (including VEGF

and ANGPTL4), which would significantly improve the quality of therapy [52]. Furthermore, *in vitro* studies have shown that attempts to pharmacologically stabilize HIF-1 effectively inhibit the angiogenic potential of UM cells.

El Filali et al. in their study demonstrated that VEGF-A expression in UM cells is strongly dependent on oxygen conditions and is much more intense under hypoxic conditions. This process is regulated by HIF-1α, further indicating its significant role in tumor progression and the development of distant metastases [53]. Kim et al. investigated the role of the methylation/demethylation cycle in stabilizing HIF-1α and the consequences of this process on tumor growth and vascularization *in vivo* in a mouse UM model. They found that the methylation/demethylation cycle is significantly involved in the process of inhibiting HIF-1α under hypoxic conditions, and mutations S28Y and R30Q in the consensus sequence SET7/9 increase the resistance of HIF-1α to degradation by methylation. The potential significance of SET7/9-dependent methylation and LSD1-dependent demethylation of HIF-1α in regulating retinal and tumor angiogenesis has been suggested, along with the consideration of using this mechanism in future oncological therapies aimed at treating UM in humans [54].

Retinoblastoma

Retinoblastoma (RB), the most common primary intraocular tumor in children, accounts for about 4% of all pediatric ocular tumors and 2.5–4% of all malignant cancers in children [55]. The global incidence varies, with estimates ranging from 1 in 16,000–20,000 live births [55, 56]. The development of the tumor is initiated by a biallelic mutation in the *RB1* gene or amplification of the MYCN oncogene. Current treatment standards include: intra-arterial, intravenous, intravitreal, or intracameral chemotherapy, transpupillary thermotherapy, radiotherapy (external beam radiotherapy and plaque radiotherapy), cryotherapy, and laser photocoagulation, with enucleation as a last resort [57]. Modern therapies encompass an expanding range of targeted actions, maintaining high survival rates while focusing on achieving the best possible visual acuity outcomes. However, the therapeutic options listed above are still associated with numerous side effects, such as retinal damage, significant loss of visual acuity, visual field narrowing, and the development of secondary cancers. There is still a need to identify additional, more effective therapeutic strategies aimed at targeting RB.

The role of HIF-1α in RB has become an active area of research in the literature. Elevated levels of HIF-1α have been reported in RB tissues [58, 59]. Furthermore, the influence of HIF-1α on tumor progression and cancer cell proliferation has been demonstrated, along with its close association with the development of pathological neovascularization, which underlies the progression and invasion of RB. Its role is based on the modulation of oxygen-dependent gene expression, influencing cell proliferation and energy metabolism [60, 61, 62]. In a study by Liu et al., it was confirmed that HIF-1α influences the progression of RB at the cellular level. Elevated levels of NEAT1 and HIF-1α were found in RB cells, while miR-106a expression was reduced in normal RB cells compared to retinal pigment epithelial cells. Increased stimulation of miR-106a inhibited HIF-1α expression, resulting in the suppression of angiogenesis [63].

Corneal neovascularization

The cornea, under physiological conditions, is a transparent structure and does not have vascularization. In the course of certain diseases, pathological blood vessels can form, spreading from the limbus toward the center of the cornea. This process causes corneal opacity and loss of transparency, ultimately leading to impaired visual acuity. Diseases in which the above-described complication may occur include autoimmune disorders, such as uveitis, chemical burns, infections, and injuries [64]. Qian Deng et al. described the protective role of inhibiting lysine-specific demethylase 1 (LSD1) through the HIF-1α pathway in the development of neovascularization, oxidative stress, and ferroptosis following alkaline corneal burn in mice. They demonstrated significantly elevated levels of LSD1 and HIF-1α in corneas damaged by alkaline burns. Furthermore, it was proven that subconjunctival injections of tranylcypromine hydrochloride (TCP), an LSD1 inhibitor, and AG490, an inhibitor of the Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) pathway, reduced corneal inflammation and neovascularization. Both inhibitors decreased HIF-1α expression, leading to anti-angiogenic and anti-stress effects. Additionally, it was inferred that LSD1 likely regulates HIF-1α through the JAK2/STAT3 pathway, which led the authors to propose it as a potential therapeutic target for CNV [65].

Neovascular form of pterygium

Pterygium is a fibrous-vascular, degenerative, non-neoplastic lesion of the conjunctiva that gradually grows onto the cornea. An advanced form of pterygium, invading the cornea and infiltrating toward its center, can significantly limit the visual field and impair vision; additionally, it may lead to the development of irregular astigmatism. Currently, the most effective therapeutic approach is based on surgical removal of the lesion; however, the recurrence rate remains significant. Recurrent pterygium may exhibit even more aggressive growth than the primary form [66]. The etiology of pterygium has not yet been fully defined. Factors believed to trigger its development, as cited in the literature, include heredity, ultraviolet light exposure, chronic inflammation, and infection with the human papillomavirus. There are reports indicating a significant role of angiogenic factors in stimulating the proliferation of fibrous vessels, whose development facilitates the formation and further invasion of pterygium into surrounding structures [67]. Meng et al. observed increased expression of VEGF and ANGPTL4 in surgically excised pterygia. Furthermore, they found that monotherapy with anti-VEGF drugs was insufficient in treating patients with pterygium. Based on these findings, the authors suggested the need for further research into therapies targeting the HIF-1 factor, which regulates angiogenic mediators such as VEGF and ANGPTL4. According to the researchers, such a multi-targeted approach could revolutionize current therapeutic strategies for this degenerative lesion [68].

CONCLUSIONS

The HIF-1 factor plays a crucial role in many neovascular eye diseases. It is involved both in initiating the disease process and in its further development. HIF-1 is a central regulator of cellular detection and adaptation to oxygen conditions, and is responsible for cellular oxygen homeostasis, erythropoiesis, angiogenesis, and mitochondrial metabolism. It plays an important role in the process of neoangiogenesis by regulating angiogenic mediators. Its involvement in neovascular eye diseases has been confirmed in the literature for conditions such as AMD, PDR, RVO, ROP, UM, RB, as well as neovascularization of the cornea or the neovascular form of pterygium. At the same time, this factor has been repeatedly proposed as a potential molecular target for future therapies for vascular diseases of the eye. This review highlights the significant importance of the HIF-1 factor in ocular diseases and demonstrates the need for further research to evaluate the complex molecular mechanisms and the role of HIF-1 in ophthalmology, as well as the possibility of utilizing it as a molecular target for innovative therapies for eye diseases.

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