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Review Article

Targeting Angiogenesis: New Horizons in Ocular Tumor Therapy

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Abstract: Angiogenesis, the formation of new blood vessels within malignant tumors, is essential for cancer growth, sustenance, and metastasis. This complex process is regulated by a variety of molecular factors and pathways, as explored in a recent comprehensive review on angiogenesis. The review highlights the regulatory mechanisms that unlock therapeutic potential, focusing on hypoxia and its role in inducing vascular endothelial growth factor (VEGF) expression, a key driver of angiogenesis. It examines the interplay between angiopoietins, fibroblast growth factors (FGFs), and endogenous inhibitors of angiogenesis, as well as the role of transmembrane adhesion proteins, such as integrins, in mediating cellular responses critical to vascular development. The review also discusses the critical role of angiogenesis in tumor growth, emphasizing how the "angiogenic switch" enables tumors to acquire an aggressive phenotype. In this context, anti-angiogenic (AAG) therapies targeting these pathways are being investigated for various cancers, including ocular malignancies. Despite the widespread use of angiogenesis inhibitors in non-malignant ocular diseases, reports of their application in ocular tumors remain limited. Evidence supports the involvement of angiogenesis in the progression and metastasis of ocular malignancies, including retinoblastoma, ocular melanoma, and Von Hippel-Lindau (VHL) disease. Preliminary studies of AAG therapies for ocular tumors, such as ocular melanoma and VHL, show promising results. However, their efficacy needs to be confirmed through well-designed, controlled clinical trials. By providing a detailed overview of the molecular underpinnings of angiogenesis and its implications for tumor growth, this review underscores the potential of targeting angiogenic pathways as a therapeutic strategy for ocular tumors and other malignancies.

Keywords: Ocular Tumor, retinal cancer, Von-Hippel-Lindau, Vasculogenesis and Tumor Therapy

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1. INTRODUCTION

The genesis and evolution of tumors rely on many pathophysiological alterations within the tumor cells and the surrounding tissue microenvironment. The unregulated proliferation of cancer cells and alterations in general cellular differentiation are evident features of cancers. The exceptional difficulties of a swiftly proliferating cell-mass conversely need supplementary needs, one of those is the attainment of a sufficient blood source. Cancer neo-angiogenesis has gained significance in indulgent cancer pathophysiology and identifying novel treatment targets. The creation of new vessels may transpire via many methods. Vasculogenesis (Vgs) refers to the creation of fresh blood vessels by the conscription of identical endothelial stem cells, known as hemangioblasts (Hgs)[1]. Hgs originate in the bone marrow and move to locations of Vgs, primarily through embryonic growth. Angiogenesis (Ags) refers to the growth of new blood vessels from pre-existing vascular structures. Ags is common throughout development, although it may also occur in adult biological processes. A third kind of neovascularization transpires when pre-existing arteries are restructured to meet novel biological requirements[2]**.** This review will succinctly examine the essential mechanisms involved in Ags, focusing on pro and anti-angiogenic (AAg) pathways, as well as the use of AAg medicines in cancer therapy and the current AAg medications.

1.1. Ags Regulation Unlocking Therapeutic Potential

Considering the significance of Ags in many illnesses such as cancer, diabetic retinopathy, and autoimmune disorders, much study has focused on the variables that govern the creation of new blood vessels. Endogenous pro- and AAg factors are produced inside tissues. There exists a delicate equilibrium between pro-angiogenic (PAg) and AAg factors that dictates the angiogenic condition of the tissue. With the exception of certain locations in adults, including the female generative structure and tissues in the process of wound healing, Ags is minimal in the nonappearance of illness[3]. The Duration to half-depletion of inhabitant endothelial cells (ECs) spans many years, making them one of the most constant cell groups[4]. Ags might be stimulated by alterations in the endothelial cell milieu, containing genetic modifications, mechanical strain, oxidative stress, trauma and hypoxia. These pathways are associated with the increase of Ags in tumor growth, initiating a cascade of downstream actions that eventually activate ECs and facilitate the production of new capillaries. Thus Ags is a tightly regulated process essential for both physiological and pathological conditions. The balance between pro and anti-angiogenic factors determines tissue angiogenic activity, with disruptions leading to diseases such as cancer and diabetic retinopathy. Understanding these mechanisms offers promising avenues for therapeutic intervention in angiogenesis-associated disorders

1.2. Hypoxia (Oxygen deficiency) Inducible Transcription Factor-1 (HIF-1)

Oxygen deficiency, or hypoxia, is one of the most well-established triggers of angiogenesis. The hypoxia-inducible factor 1 (HIF-1) plays a central role in this process. HIF-1 is a heterodimeric transcription factor composed of two subunits: HIF-1α and HIF-1β. Under hypoxic conditions, HIF-1α becomes stabilized and binds to hypoxia-response elements (HREs) within the promoters of target genes, driving the transcription of pro-angiogenic proteins such as vascular endothelial growth factor (VEGF) and its receptor VEGFR-1[5]. These factors promote the growth of new blood vessels in response to oxygen scarcity. In contrast, under normal oxygen conditions, HIF-1α undergoes hydroxylation by oxygen-dependent enzymes, requiring ferrous iron or 2-oxoglutarate as cofactors. This modification allows HIF-1α to associate with the von Hippel-Lindau (VHL) tumor suppressor protein, marking it for degradation and thus preventing its binding to HREs, effectively silencing its transcriptional activity under normoxic conditions. This sophisticated regulatory mechanism ensures that angiogenesis is activated only in response to genuine tissue hypoxia.

1.3. Endothelial Growth Factor and relations

The vascular endothelial growth factor (VEGF) family consists of five merged variants of VEGF and three on the other hand merged variants of PlGF. Affiliates of this intimate have pleiotropic functions in the creation of original vessels. Initially identified as vascular permeability factor, VEGF-A enhances endothelial cell fenestrations and induces vascular leakage. VEGF isoforms enhance endothelial cell proliferation, migration, death, and vascular tube formation. VEGF-B, C and D possess heparin-binding domains and are sequestered within the extracellular matrix, while VEGF-A and E may disperse freely following release. VEGF is created by many cancer cell types, immune cells, smooth muscle cells, mesangial cells, keratinocytes, astrocytes, and osteoblasts[6]**.** To elicit biological effects, VEGF isoforms associate with a group of tyrosine kinase receptors known as VEGF receptors (VEGFR-1 to 3). VEGFR-1 and 2 are present on the surface of ECs, with VEGFR-2 activation resulting in the most significant enhancement in Ags[7]. VEGF may bind to neuropilin receptors, activating ECs to induce Ags. The countenance of VEGF isoforms, VEGFR, and neuropilin receptors varies across tumor cell types and endothelial cell populations, perhaps explaining the disparate amounts of Ags seen in these systems[8]**.** The VEGF family, with its diverse isoforms and receptors, plays a central role in angiogenesis by regulating endothelial cell behaviors such as proliferation, migration, and vascular formation. The interaction between VEGF isoforms, VEGF receptors, and neuropilin receptors contributes to the complex regulation of angiogenesis in both normal and tumor tissues. The variability in expression of these molecules across different cell types may help explain the differences in angiogenesis observed in various tumor systems, highlighting potential therapeutic targets for anti-angiogenic strategies.

1.4. Angiopoetins

Angiopoetins seem to regulate Ags in conjunction with VEGF. Ang-1 interacts with the tyrosine kinase receptor, tie-2, to facilitate endothelial cell sprouting and maturation. Ang-2 interacts to the same Tie-2 receptor, resulting in the depletion of pericytes, hence exposing ECs to adjacent angiogenic stimuli[9]. The varied effects of the same receptor are elucidated by ang-1 binding inducing phosphate incorporation of the tie-2 receptor, but ang-2 binding promotes dephosphorylation of the same receptor. In the deficiency of VEFG, ang-2 induces the regression of undermined vasculature; nevertheless, when VEFG is present, Ags is promoted[10]**.** The differential effects of Ang-1 and Ang-2 on the Tie-2 receptor, through phosphorylation and dephosphorylation, highlight the complex mechanisms governing vascular development. In the absence of VEGF, Ang-2 induces vascular regression, but in its presence, angiopoetins promote angiogenesis, emphasizing

their pivotal role in vascular dynamics and therapeutic potential.

1.5. Fibroblast Growth Factors (FGF)

FGF 1 and 2 are heparin-binding growth factors that serve as powerful stimulators of Ags. To enhance Ags, it is necessary to release these heparin-bound substances from the extracellular matrix. These particles attach to FGF receptors on ECs, stimulating ECs proliferation, facilitating ECs differentiation, and acting as a chemoattractant for ECs[11]. Proteolytic enzymes, Matrix metalloproteinases (MMPs) constitute a substantial group (exceeding 20 members) of proteolytic enzymes with diverse impacts on Ags[12]. The most well-characterized proteases that regulate tumor Ags are MMP 2 and 9. PAg MMPs may also facilitate the release of matrix-bound-growth-factors and the protein degradation of endogenous AAg compounds[13]. Nonetheless, there exists a category of AAg MMPs, such as MMP-7, that function to impede vascular development. Mice deficient in MMP-7 have a more pronounced neovascular response to angiogenic stimulation. The exact method of the AAg function remains unclear; nevertheless, there is evidence supporting the production of antiangiogenic chemicals via matrix degradation[14]. Endogenous tissue inhibitors of MMPs have AAg functions. The plasminogen activator family of serine peptidases and their inhibitors have remained associated with the control of Ags. The equilibrium between protease cell interaction and the quantity of endogenous plasminogen inhibitors governs this intricate system. Eventually, the initiation of these mechanisms in neoplastic cells facilitates Ags and an invasive cancer phenotype.

1.6. Endogenous Inhibitors of Ags

More than fifteen endogenous Ags inhibitors remained found. The significance of these inhibitors' "weight" is crucial in shifting the equilibrium against Ags in the majority of grown tissue types. Numerous antagonists are produced as proteolytic peptides of proteins that, in their intact form, do not contribute to Ags[15]. Angiostatin, perhaps the most well-defined endogenous Ags inhibitor, is generated by the breakdown of plasminogen by matrix MMPs. The active angiostatin molecule consists of four repeating kringle domains that provide AAg action. Despite the enigmatic nature of angiostatin's processes, it functions as a potent suppressor of endothelial cell growth, movement, and tube development. Endostatin, a proteolytic peptide derived from collagen XVIII, appears to be a more effective suppressor, potentially acting through mechanisms akin to those of angiostatin. Additional endogenous Ags inhibitors including thrombospondin, Platelet factor-4, SPARC, anti-thrombin III and PEX[16]**.**

1.7. Transmembrane adhesion proteins- Integrins (Igs)

Igs are heterodimeric membrane proteins that facilitate cell signaling via exchanges with the extracellular matrix. Igs α5β3 and α5β5 have been identified in active ECs. Antibodies targeting α5β3 have shown the ability to suppress Ags, indicating that these molecules are significant contributors to the process and refuting the idea that Igs are just indicators of Ags. Subsequent investigations elucidating the function of these particles in other systems and sensation animals have shown inconsistent results, rendering the actual role of these molecules rather ambiguous[17]**.** Further research is needed to fully understand the role of Igs α5β3 and α5β5 in cell signaling and their potential as therapeutic targets. Despite the conflicting results in different systems, it is clear that these molecules play a crucial role in regulating immune responses and cell behavior. By unraveling the complexities of Igs, scientists may be able to develop more effective treatments for a variety of diseases and disorders. With continued research, scientists may be able to uncover the specific mechanisms by which Igs α5β3 and α5β5 influence cell signaling and immune responses. This knowledge could lead to the development of targeted therapies that manipulate these molecules to treat conditions such as autoimmune diseases, cancer, and inflammation. By understanding the role of Igs in cell behavior, researchers may also be able to design novel strategies to modulate immune responses and improve overall health outcomes for patients. Ultimately, further investigation into the function of these particles holds great promise for advancing medical science and improving patient care.

1.8. Ags and Tumor Growth

Tumor proliferation generally starts by passive diffusion, facilitating the acquisition of oxygen. As tumors grow, they need an independent blood supply and the formation of new arteries to provide oxygen, nutrients, and eliminate cellular waste products. The phrase "angiogenic switch (AgSw)" denotes the intricate set of variables modified to facilitate tumor Ags[18]. Ags in tumors markedly varies from that in physiological settings, since tumor Ags is more vigorous and necessitates more endothelial cell proliferation. Tumor therapy often employs mixtures of cytotoxic medicines to specifically target rapidly proliferating cells while minimizing harm to non-tumor tissues. Owing to variations in tumor Ags, malignancies are frequently influenced by Ags inhibitors. Medical and laboratory investigations have exposed the absence of systemic toxicity of endostatin and angiostatin in both people and animals. Tumor Ags might potentially mitigate the issue of tumor treatment confrontation often perceived with cytotoxic drugs[19]. ECs exhibit heterogeneity, perhaps rendering some subpopulations insensitive to certain therapies. Various resistance mechanisms may persist, including the differential production of PAg molecules by tumor cell subpopulations or compensatory responses to the absence of certain growth factors. Hypoxia may activate the AgSw, serving as a significant stimulator of tumor Ags. Ags in malignancies is facilitated by Vgs, which involves the recruitment of endothelial cell precursors generated from bone marrow. Genetic instability and mutations in tumor cells may potentially induce Ags. The sequential activation of oncogenes in tumor cells influences their PAg capabilities. Assessing Ags and angiogenic factors such as VEGF may provide significant insights into tumor therapy. Immuno-histochemical endothelial markers may assist in quantifying micro vessel count and density for a particular tumor[20].

2. AAG TUMOR THERAPIES

More than 60 AAg treatments have remained investigated in clinical studies. Notwithstanding the many studies, only one drug, bevacizumab, has received FDA approval for usage in conjunction with predictable chemotherapy for the action of metastatic colon cancer[21]. Other potential AAg treatments are still undergoing clinical trials to determine their effectiveness and safety for various types of cancer. The approval of bevacizumab marks a significant milestone in the advancement of targeted cancer therapies, but researchers continue to explore new AAg treatments in the hopes of finding more

effective options for patients with advanced cancer. The ongoing research in this field shows promise for the development of additional approved AAg treatments in the future. The existing spectrum of AAg medicines may be categorized as either direct or indirect action. While it is true that AAg treatments are still being researched, but fails to acknowledge the potential limitations and side effects that may arise from these new treatments, which could impact their overall effectiveness. Categorizing AAg medicines as either direct or indirect action oversimplifies the complexity of cancer treatment and fails to consider the individualized nature of patient care. Direct-acting medicines target ECs to inhibit neovascularization, while indirect drugs influence angiogenic factors that subsequently modify endothelial cell function[22]. While direct-acting AAg medicines may seem more straightforward in their approach, the potential side effects and limitations of these treatments must be carefully considered. Indirect-acting drugs, on the other hand, may offer a more nuanced and personalized approach to cancer treatment by targeting specific angiogenic factors. It is important for researchers and healthcare providers to continue studying and evaluating both types of AAg treatments to ensure that patients receive the most effective and tailored care possible.

2.1. VEGF Pathway Modulation

Various tumor cells produce significant amounts of VEGF, and the VEGF-driven angiogenic pathway has been a key target in pharmacological research. These therapeutic approaches are indirect, as they rely on altering a tumor-derived angiogenic signal rather than directly influencing endothelial cell activity. Several strategies have been developed to regulate VEGF ligand signaling. Bevacizumab, a monoclonal antibody, neutralizes VEGF. VEGF levels can also be lowered through VEGF-traps, which are genetically engineered decoy receptors derived from VEGFR domains[23]. Antisense RNA and RNA interference have been employed to block VEGF production by cancerous cells. Other methods focus on the VEGFR family. Monoclonal antibodies targeting VEGFR2 can prevent VEGF ligand binding and subsequent activation of Ags. Ribozymes, designed to degrade mRNA for VEGFR, may reduce cellular VEGFR levels[24]. Various small molecules, more suitable for pharmaceutical use, have been developed to specifically inhibit VEGFR kinase activity, thereby blocking its signaling pathways. Despite promising pre-clinical statistics and a favorable side effect profile relative to standard chemotherapy, oral VEGFR inhibitors have not demonstrated a statistically superior treatment efficacy in clinical trials[25].

2.2. MMP-Inhibitors

The relatively non-specific MMP inhibitor, marimastat, can be administered orally. This drug has been tested in numerous Phase I and II trials, as well as one Phase III trial, for treating pancreatic cancer. While marimastat may be administered orally, its efficacy in treating pancreatic cancer has not been definitively proven, as evidenced by the lack of FDA approval after multiple trials. The broad inhibition of MMPs by marimastat could lead to off-target effects and potential harm to patients. Further research is needed to determine if the potential benefits of marimastat in treating pancreatic cancer outweigh the risks associated with its non-specific inhibition of MMPs. More targeted MMP inhibitors may offer a safer and more effective alternative for patients with this aggressive form of cancer. Combination therapy with marimastat and other drugs may be explored to enhance its therapeutic effects while minimizing potential harm. However, marimastat's musculoskeletal toxicity has been significant (44% in one study), limiting its clinical application. More selective MMP inhibitors are currently in development and may have fewer side effects[26]. These new inhibitors may hold promise for effectively targeting MMPs in pancreatic cancer without causing significant musculoskeletal toxicity. Researchers are hopeful that these more targeted therapies will provide a safer and more effective treatment option for patients with this challenging disease. As clinical trials progress, the potential for combination therapies to further enhance the effectiveness of MMP inhibitors in treating pancreatic cancer continues to be explored.

2.3. Endogenous Peptide Inhibitors

Endostatin and Angiostatin have both undergone Phase I clinical studies. These drugs exert direct and specific effects on activated endothelium, especially that which is not alleviated by pericytes. This exactness has shown an excellent safety record with few to absent systemic adverse effects. Endostatin has more potency than angiostatin and may be delivered via intravenous or subcutaneous routes. The unstable characteristics of peptide medicines and the need for vaccination may restrict their long-term efficacy as cancer therapies[27].

2.4. Integrin Blocking Drugs

In light of the data supporting integrin α5β3 and α5β5 indicating in the enhancement of Ags, anti-integrin drugs are developed. Vitaxin is an anti-α5β3 antibody that inhibits integrin activity. This chemical obstructs bFGF-induced Ags. SCH-221153 inhibits both α5β3 and α5β5 integrins via interacting with shared signaling regions. While successful in animal tumor models, research in humans is constrained[28]. Clinical trials are still ongoing to determine the efficacy of anti-integrin drugs in human patients. The potential for these drugs to inhibit tumor growth and metastasis is promising, but further research is needed to fully understand their effects on human biology. Despite the current limitations, the development of anti-integrin drugs represents a significant advancement in the field of cancer treatment and holds great potential for improving patient outcomes. As researchers continue to study the effects of anti-integrin drugs in human patients, they are also exploring potential combination therapies to enhance their effectiveness. By targeting multiple signaling pathways involved in tumor growth and metastasis, these drugs may offer a more comprehensive approach to cancer treatment. Ultimately, the hope is that anti-integrin drugs will not only help to slow or stop tumor progression but also improve overall survival rates for patients battling cancer.

2.5. Thalidomide

Thalidomide, a synthetic derivative of glutamic acid, has shown an AAg property. Its efficacy in addressing high-grade gliomas and plasma cell malignancies has been constrained. Ags inhibitors, which have tumoristatic properties, have been used as monotherapy in clinical studies; nonetheless, their efficacy has been suboptimal[29]. These inhibitors are expected to be used in conjunction with other chemotherapies; nevertheless, the outcomes of extensive clinical studies have not been notably favorable. Antiangiogenic medicines have varying effects in small vs big tumors and might not be applicable for

the appropriate disease stage. Certain writers propose that AAg treatment could be optimally used as chemo preventive medicines. The suboptimal outcomes of AAg treatment may stem from resistance mechanisms, necessitating combination with conventional chemotherapy and additional Ags inhibitors. Not all cancers exhibit the same AgSw or stimulate Ags uniformly. Gene profiling is progressing to customize AAg therapy for individual malignancies, since the appearance patterns of Ags molecules may facilitate tailored therapies[30].

3. AAG THERAPY FOR OCULAR TUMORS (OTS)

AAg therapy is already included in the ophthalmologist's therapeutic arsenal, exemplified by Macugen (anti-VEGF aptamer) treatment for the "wet" variant of age-related macular degeneration[31]. As clinical trials continue to explore the potential of anti-angiogenic therapies in ocular oncology, the future looks promising for patients with these challenging conditions. The success of treatments like Macugen in age-related macular degeneration serves as a testament to the potential of AgSw-targeted therapies in the field of ophthalmology. AAg therapy is expected to contribute significantly to the treatment of various OTs as the efficacy of AAg inhibitors enhances. These advancements in anti-angiogenic therapies offer hope for patients with ocular tumors, as they provide a targeted approach to treating these challenging conditions. As the efficacy of AAg inhibitors continues to improve, the potential for these treatments to become a standard in ophthalmology is promising. By focusing on tumors where AAg therapy has shown success and where it holds the greatest potential, researchers can continue to advance the field of ocular oncology and improve outcomes for patients.

3.1. Uveal Melanoma

"Tapper and co-authors used angiogenic factors as markers for uveal melanoma, examining aspirates from the anterior chamber of eyes undergoing ophthalmic surgery[32]. Their findings revealed that seven out of eleven eyes with confirmed uveal melanoma showed a positive angiogenic response in this assay, while only one out of fifteen eyes undergoing routine cataract surgery tested positive. In vitro studies of uveal melanoma cell lines further demonstrated the production of angiogenesis-regulating factors. All seven cell lines expressed VEGF (both mRNA and protein) and Ang-2 (mRNA), while only one cell line produced angiostatin from plasminogen. Given that uveal melanoma spreads via the bloodstream, it has been hypothesized that the tumor's vascularity and the production of proangiogenic molecules might be linked to metastasis. In one study, tissue samples from 61 eyes enucleated due to melanoma were analyzed using Ulex europaeus agglutinin I staining, a marker for endothelial cells. Vascular density at the tumor's apex, center, and base was measured, but no significant difference was observed between metastatic (30 eyes) and non-metastatic (33 eyes) tumors[33]. Vasculogenic mimicry (VgM) is a process where uveal melanoma cells adopt vascular cell characteristics, with tumor cells expressing genes commonly found in both embryonic and adult vasculatures. Within these tumors, channels capable of maintaining fluid flow are formed, though they lack endothelial cells. It remains unclear if anti-angiogenic (AAg) therapies can effectively target these non-endothelial vessels. Endostatin, a strong AAg molecule, was ineffective against vessels formed through VgM. Therefore, drugs with dual mechanisms targeting both types of vessels or new drugs specifically designed to target VgM may be needed. Only one case of AAg therapy for uveal melanoma has been documented. An 8-year-old patient with metastatic ocular melanoma was initially treated with a combination of IL-2 and thalidomide, which stabilized the metastatic disease in her liver and pancreas for 23 months. When lung lesions later developed, another round of IL-2 therapy further stabilized her disease for 18 months[34]. Her survival with this treatment, totaling over 41 months, far exceeds the typical 2 to 5 months of average survival. Although there is evidence that ocular melanoma cells produce angiogenic factors and can support ECs proliferation, it is still unclear whether tumor vascular density or VEGF expression reliably predict metastasis. Larger trials, including those focused on adult tumors, will be necessary to assess the effectiveness of AAg inhibitors in treating ocular melanoma[35].

3.2. Retinoblastoma

Retinoblastomas generate PAg factors in relation to uveal melanoma. In the similar investigation, Tapper and co-author assessed ocular fluids containing retinoblastoma using their chick embryonic membrane test. Nine out of ten tumors were found to be positive[36]. The specific chemicals accountable for this PAg response remain unambiguously unidentified. Micro-vascular density has been assessed for its influence on tumor performance and metastasis. A research including 107 retinoblastoma patients assessed vascular density using CD31 immunohistochemistry. An increased level of vascularization was associated with incursion into the choroid or optic nerve. The 18 metastasized tumors exhibited significantly elevated microvascular density compared to non-metastasized tumors[37]. In a comparable study including 25 eyes, researchers used CD34 to identify and quantify tumor vascular area. An expanded vascular region was associated with elevated metastatic potential, and according to the author's threshold, the measurement exhibited 99% sensitivity and 80% specificity in forecasting disease propagation[38]. Despite retinoblastoma being a viable target for AAg treatment, no clinical studies including Ags inhibitors have been conducted. A more comprehensive knowledge of the specific variables generated by these tumors may expedite the use of AAg drugs. In a transgenic mouse retinoblastoma model, vitamin D have shown to reduce tumor Ags. The therapeutic significance of these discoveries remains uncertain[39].

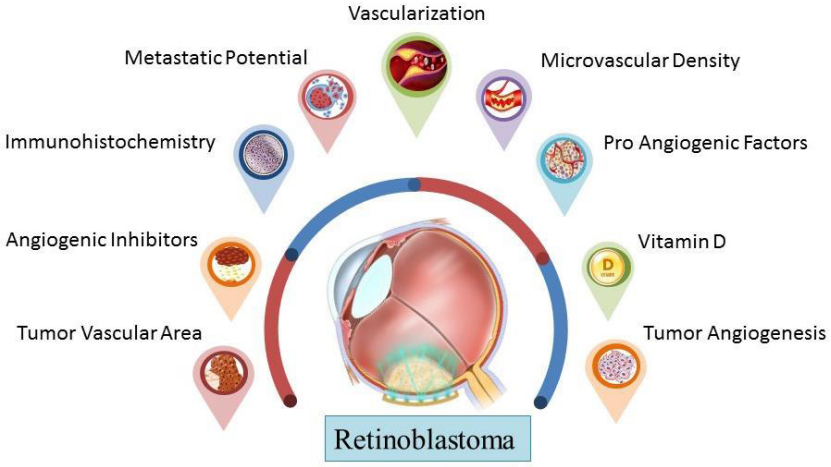

Fig 1: Key Factors and Mechanisms Involved in Retinoblastoma Progression

3.3. Von Hippel-Lindau Disease (VHL)

The molecular foundation of VHL illness has been elucidated and is partially attributed to unregulated mechanisms of the Ags system. The VHL-protein functions as a cancer inhibitor by binding to HIF-1, potentially leading to its degradation, so inhibiting the stimulation of PAg genes. In VHL illness, the synthesis of PAg factors, primarily VEGF, remains unregulated owing to the absence or dysfunction of VHL protein. These results provide a possible molecular target for AAg treatment[40]. Numerous case studies about the therapy of ocular VHL were documented. SU-5416, a VEGFR inhibitor, was administered to a 30-year-old lady with retinal hemangioblastomas that did not respond to standard treatment and had diminished vision due to macular edema. The VEGFR inhibitor presumably functioned largely to diminish the vascular permeability of the tumor vasculature and would probably be tumoristatic in any scenario. A second trial of SU-5416 involving six individuals, of whom only two exhibited a helpful reaction to therapy, was conducted on an individual with multifocal VHL, including retinal lesions resistant to conventional laser therapy. This trial resulted in complete regression of the lesion within ten months and stabilization of vision at 20/20 in the affected eye[41]**.** While the results of this trial are promising, a larger sample size is needed to determine the overall effectiveness and safety of SU-5416 in treating multifocal VHL with retinal lesions. Long-term follow-up is necessary to assess any potential side effects or recurrence of the lesions. A third group of researchers has used this same AAg agent to address an invasive hemangioblastoma situated in the optic nerve head. Despite SU5416 not producing a quantifiable reduction in lesion size, the patient in this case report had enhancements in both visual acuity and visual field. This suggests that the AAg agent may have potential benefits beyond solely reducing tumor size. Further studies are needed to fully understand the mechanisms behind these improvements and to determine if AAg therapy could be a viable treatment option for other optic nerve head tumors. The results of this case report highlight the importance of exploring alternative treatment options for rare and difficult-to-treat tumors like hemangioblastomas. Despite the positive outcomes associated with SU5416 in treating ocular hemangioblastomas in VHL, we anticipate a bigger randomized study to evaluate its effectiveness relative to conventional therapies[42].

3.4. Metastatic Disease

The majority of comprehensive studies for antiangiogenic tumor treatment have been conducted for diseases often seen in extraocular locations. The eye may serve as a location for metastasis from many malignancies. The management of metastatic malignancies includes possible ocular sites in addition to the main tumor location. A 44-year-old woman with metastatic breast cancer affecting four locations (bone, liver, eye and lung) was administered TNP-470, a powerful Ags inhibitor. Her illness exhibited restricted regression for three months, monitored by stability and sustained eminence of life for five months[43]**.** The documentation of ocular reactions to Ags inhibitors in metastatic illness may be constrained owing to insufficient monitoring of ocular malignancies in the majority of investigations.

4. CONCLUSION

Despite the need of Ags for tumor development, conservation, and metastasis, only one AAg agent has been licensed for use in amalgamation treatment. Numerous inhibitors remain under research, and advancements in these compounds, along with our capacity to identify the most effective medicines for certain tumors, are expected to progress. The use of Ags inhibitors for ocular cancers is currently underdeveloped; however, as AAg tumor therapy progresses, an increased utilization of AAg treatment in ophthalmology is anticipated.

5. AUTHORS CONTRIBUTION STATEMENT

Prof Dr. Ammar A. Razzak Mahmood wrote the initial draft. Dr. Anand Mohan Jha, Dr. John Abraham contributed to critical revision and supervision. Finally, Dr. Laishram Elizabeth Devi has reviewed the article. All authors reviewed the manuscript.

6. CONFLICT OF INTEREST

Conflict of interest declared none.

Abbreviations

hemangioblasts (Hgs)
Von-Hippel-Lindau (VHL)
anti-angiogenic (AAg)
Angiogenesis (Ags)
metalloproteinases (MMPs).
Vasculogenesis (Vgs)
angiogenic switch (AgSw)
Vasculogenic mimicry (VgM)
pro-angiogenic (PAg)
endothelial cells (ECs)
Integrins (Igs)
ocular tumors (OTs)

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