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Comparative Angiogenesis-Related Pathologies in Humans, Dogs, and Cats: Mechanisms, Biomarkers, and Therapeutic Perspectives

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ABSTRACT

***Background*:** Angiogenesis is a tightly regulated biological process essential for embryonic development, tissue repair, and vascular homeostasis. Dysregulated angiogenesis contributes to numerous pathological conditions, including cancer, retinal disorders, chronic inflammatory diseases, and ischemic injury. Although angiogenic mechanisms have been extensively characterized in humans, comparative information in companion animals remains fragmented despite the increasing clinical importance of angiogenesis in veterinary oncology, ophthalmology, and internal medicine. This review aimed to provide a comprehensive comparative synthesis of angiogenesis-related diseases in humans, dogs, and cats, emphasizing conserved and species-specific molecular pathways, biomarkers, diagnostic approaches, therapeutic strategies, and translational significance within the One Health framework.

***Review*:** This review summarizes the physiological regulation of angiogenesis and compares major molecular mediators, including VEGF, FGF, angiopoietins, PDGF, HIF-1α, matrix metalloproteinases, and endothelial-pericyte interactions across species. Comparative evidence demonstrates that VEGF-centered signaling is highly conserved in humans, dogs, and cats, whereas important interspecies differences exist in gene expression, receptor activity, vascular architecture, biomarker availability, and therapeutic responses. Tumor-associated angiogenesis is examined using human solid cancers, canine hemangiosarcoma, and canine and feline mammary tumors as representative models, highlighting common mechanisms of hypoxia-driven vascular remodeling while emphasizing species-specific pathological characteristics. Ocular angiogenic disorders, including diabetic retinopathy, age-related macular degeneration, hypertensive retinopathy, progressive retinal atrophy, and retinal inflammatory diseases, are discussed from comparative anatomical and translational perspectives. The review further evaluates inflammatory and ischemic angiogenesis in rheumatoid arthritis, inflammatory bowel disease, myocardial ischemia, feline chronic gingivostomatitis, chronic enteropathies, and wound healing. Current angiogenesis-related biomarkers, including VEGF, angiopoietins, soluble VEGF receptors, and HIF-1α, together with immunohistochemistry, ELISA, molecular techniques, OCT/OCT-A, Doppler ultrasonography, and contrast-enhanced ultrasound, are critically compared regarding their diagnostic utility and limitations in veterinary medicine. Human anti-angiogenic therapies, including bevacizumab, ranibizumab, aflibercept, and tyrosine kinase inhibitors, are contrasted with current veterinary applications such as toceranib phosphate and emerging experimental approaches. Remaining challenges include limited species-specific reagents, insufficient biomarker validation, lack of standardized diagnostic protocols, restricted clinical trial infrastructure, and the need for expanded canine and feline omics resources.

***Discussion*:** Comparative evaluation demonstrates that companion animals naturally develop angiogenesis-associated diseases closely resembling human disorders, supporting their value as translational models. However, meaningful species-specific biological differences preclude direct extrapolation of human data to veterinary medicine and underscore the necessity for dedicated veterinary investigations. Future progress will depend on the development of species-specific diagnostic reagents, integrated multi-omics analyses, advanced imaging technologies, collaborative clinical studies, and One Health research networks. Strengthening comparative angiogenesis research will improve diagnostic precision, facilitate the development of novel therapeutic strategies, and accelerate bidirectional translation between human and veterinary medicine.

Keywords: angiogenesis, comparative pathology, VEGF, companion animals, tumor microenvironment, One Health

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I. INTRODUCTION

Angiogenesis, the formation of new blood vessels from pre-existing vasculature, is a vital physiological process essential for embryonic development, tissue repair, and wound healing. In adults, angiogenesis remains largely quiescent under normal conditions but can be reactivated during physiological processes like the menstrual cycle or pathological conditions such as cancer, chronic inflammation, and retinal diseases. The tightly regulated balance between pro-angiogenic and anti-angiogenic factors determines vascular homeostasis; disruptions in this balance can lead to either excessive or insufficient neovascularization, contributing to a variety of diseases [18,67].

In human medicine, angiogenesis has been extensively studied in the context of oncogenesis, ischemic diseases, diabetic complications, and age-related macular degeneration (AMD). The identification of key molecular drivers, such as vascular endothelial growth factor (VEGF), fibroblast growth factors (FGFs), angiopoietins (Ang1, Ang2), and matrix metalloproteinases [MMPs], has led to the development of targeted anti-angiogenic therapies. Anti-VEGF agents such as bevacizumab, ranibizumab, and aflibercept have become standard of care in ophthalmology, particularly for neovascular retinal diseases [7,79], and bevacizumab is also widely used in oncology [24,34].

In contrast, veterinary research into angiogenesis - particularly in companion animals such as dogs and cats - has only recently begun to attract significant attention. Studies have identified elevated plasma VEGF levels in canine hemangiosarcoma and VEGF overexpression in feline mammary carcinomas [12,15]. Additional work has explored the involvement of angiogenic pathways in chronic inflammatory conditions such as inflammatory bowel disease, where VEGF-A has been shown to link angiogenesis and inflammation [85]. In contrast, severe immune-mediated oral inflammatory diseases such as feline chronic gingivostomatitis have been discussed primarily in the context of immune dysregulation, and the contribution of angiogenic pathways remains speculative. However, the available data remain scattered, and comprehensive comparative studies are lacking. Despite sharing many physiological and molecular similarities with humans, dogs and cats have unique angiogenic profiles and disease susceptibilities that warrant species-specific investigation.

Given the increasing prevalence of chronic and neoplastic diseases in aging pet populations, understanding the role of angiogenesis in veterinary pathophysiology is both timely and essential. Comparative pathology offers a unique opportunity to align human and veterinary research, uncover conserved and divergent mechanisms, and enhance translational medicine initiatives. Companion animals can serve as spontaneous models of human diseases, reflecting real-world disease complexity better than traditional rodent models [95].

This review aims to synthesize current knowledge on angiogenesis-related pathologies in humans, dogs, and cats. We will explore the physiological and

molecular basis of angiogenesis, analyze its role in cancer, ocular disease, inflammation, and ischemia, and assess diagnostic and therapeutic strategies across species. Through a comparative approach, we seek to highlight both the shared molecular signatures and the species-specific differences that can inform better diagnostics, treatments, and translational research paradigms.

Previous experimental studies by the author have investigated key mechanisms relevant to angiogenesis-related pathology, including endothelial barrier dysfunction, vascular leakage, pericyte apoptosis, angiopoietin-Tie2 signaling, inflammatory cytokine-mediated vascular injury, and diabetic retinopathy-associated microvascular damage [40,42,70, 103-109]. These studies provide a mechanistic basis for the present comparative review and support the discussion of conserved vascular pathways across human and veterinary diseases.

II. PHYSIOLOGICAL AND MOLECULAR MECHANISMS OF ANGIOGENESIS

Angiogenesis is orchestrated through a complex interplay of pro- and anti-angiogenic signals that regulate endothelial cell activation, proliferation, migration, and tube formation. While the fundamental mechanisms of angiogenesis are highly conserved among mammals, notable species-specific variations exist, particularly in gene expression patterns and responses to hypoxia. Understanding these differences is essential for accurate cross-species extrapolation in both basic and translational research.

1. VEGF signaling

Under normal physiological conditions, angiogenesis is tightly regulated by several growth factors and signaling molecules. Among them, vascular endothelial growth factor (VEGF) is the most potent and well-characterized angiogenic cytokine. VEGF-A binds primarily to VEGFR-2 on endothelial cells, promoting vascular permeability, proliferation, and survival [71]. Other members of the VEGF family, including VEGF-B, VEGF-C, and VEGF-D, contribute to tissue-specific angiogenesis and lymphangiogenesis.

Fibroblast growth factors (FGFs), particularly FGF-2 (basic FGF), play a critical role in the early stages of neovascularization by stimulating endothelial cell proliferation and matrix remodeling [87].

Platelet-derived growth factor (PDGF), especially the PDGF-BB isoform, is crucial for pericyte recruitment and vessel maturation [32]. In addition, matrix metalloproteinases (MMPs) such as MMP-2 and MMP-9 facilitate angiogenesis by degrading extracellular matrix (ECM) components, allowing endothelial cells to migrate and form new capillary structures [81].

These angiogenic regulators operate in a tightly coordinated cascade, influenced by oxygen tension, inflammatory cues, and ECM composition. A comparative overview of these molecular pathways across species is presented in Table 1.

Although angiogenic pathways are evolutionarily conserved, important interspecies differences exist in gene regulation, receptor sensitivity, and pathway dominance.

Comparative studies suggest that species-specific differences exist in the expression patterns of VEGF isoforms and their receptors. For example, canine hemangiosarcomas exhibit robust overexpression of VEGF-A and VEGFR-2, similar to patterns observed in human angiosarcomas, although direct comparisons of promoter activity and hypoxic regulation remain limited [75]. In contrast, some studies have suggested that feline mammary carcinomas may exhibit limited VEGF-C-associated lymphangiogenic activity, as indicated by VEGF-C and VEGFR-3 expression studies in feline mammary tumours [84], although direct comparative data with canine or human tumours are currently limited.

Embryonic and postnatal vascular development is governed by similar cues in humans, dogs, and cats. Nonetheless, temporal expression patterns of angiogenic genes can vary. During neonatal brain development, VEGF-A expression increases, as demonstrated by studies examining its temporal expression profile; however, direct cross-species comparative data assessing whether this peak occurs earlier in dogs than in humans remain limited [6].

2. Angiopoietin-Tie2 signaling

The angiopoietin family - Ang1 and Ang2 - also plays a key role by interacting with the Tie2 receptor. Ang1 promotes vascular stabilization and pericyte-endothelial interactions, while Ang2 facilitates vessel destabilization, thereby enabling VEGF-driven sprouting [2].

Table 1. Cross-Species comparison of angiogenesis regulators.

Pathway/Factor	Human	Dog	Cat
VEGF-A / VEGFR2 axis	Key driver of angiogenesis in tumors and retinal diseases. VEGF-A upregulation leads to endothelial proliferation and increased permeability via VEGFR2.	Highly expressed in hemangiosarcoma (HSA) and other tumors. Strong correlation with malignancy and microvessel density.	Limited feline-specific data; VEGF detection reported in select neoplastic/ocular conditions, but systematic profiling is lacking.
HIF-1α response	Upregulated under hypoxia; stimulates VEGF transcription. Central to ischemia-induced angiogenesis.	Increased in myocardial ischemia and some tumors. Functions as upstream regulator of VEGF.	Stabilized under chronic inflammation; inferred role in VEGF induction.
Angiopoietin-Tie2 pathway	Ang1 binds Tie2 to promote vascular stability. Ang2 acts as antagonist, facilitating vessel remodeling.	Sparse research; presumed similar function. Tie2 detected in limited endothelial studies.	Feline endothelial Ang/Tie2 signaling: scarce data; functional studies and validated reagents are limited.

3. HIF-1α-mediated hypoxia responses

The HIF-1α transcription factor regulates VEGF under hypoxic conditions. While the HIF-1α pathway is active in all mammals, its stabilization kinetics and downstream gene activation differ. In dogs, increased HIF-1α expression has been observed in myocardial tissues with cardiac disease, suggesting hypoxia-associated activation, although its specific response to transient ischemia remains to be fully characterized. In cats, HIF-1α expression has been reported in chronic inflammatory and ischemic conditions; however, species-specific differences in stabilization kinetics and downstream signaling remain incompletely characterized. These differences may influence angiogenesis in ischemic or inflammatory conditions across species.

4. Pericyte-endothelial interactions

Pericyte coverage and communication with endothelial cells are essential for vascular stability. In both humans and companion animals, PDGF-B/PDGFR-β signaling facilitates pericyte recruitment. Although previous studies have described retinal vascular architecture using advanced imaging techniques, particularly in humans [1], direct evidence comparing pericyte-to-endothelial cell ratios between dogs and humans - or demonstrating reduced pericyte coverage in the canine retina - remains limited. Pericyte loss is particularly important in retinal microvascular disease, where it contributes to endothelial instability, vascular leakage, and breakdown of the blood-retinal barrier. Previous studies have shown that angiopoietin-2, inflammatory cytokines, and altered endothelial-pericyte signaling can promote pericyte apoptosis and microvascular dysfunction, whereas protective factors such as hepatocyte growth factor and interleukin-4 may help preserve pericyte survival and endothelial barrier integrity [40,42,70,103,105,106,108,109].

III. TUMOR-ASSOCIATED ANGIOGENESIS

Angiogenesis is a hallmark of cancer, supporting tumor growth beyond the oxygen diffusion limit [often described as ~1-2 mm in diameter], and facilitating metastasis. The tumor microenvironment (TME) induces sustained angiogenic signaling through hypoxia, inflammation, and oncogene-driven pathways. Understanding the mechanisms of tumor-associated angiogenesis (TAA) in both humans and companion animals provides crucial insight into disease progression and informs therapeutic strategies across species.

1. Human cancers

In human oncology, angiogenesis plays a critical role in the progression of solid tumors such as colorectal cancer, breast cancer, non small cell lung carcinoma, and glioblastoma multiforme. Tumor hypoxia upregulates HIF 1α, which in turn promotes VEGF

and other pro angiogenic factor expression, triggering endothelial cell proliferation, matrix degradation, and new capillary sprouting. These processes often result in disorganized, leaky, and immature vasculature [98].

The clinical development of anti-angiogenic therapies has resulted in the approval of several agents by the U.S. Food and Drug Administration [FDA]. One of the most widely used anti-angiogenic agents is bevacizumab [Avastin], a monoclonal antibody targeting VEGF-A. It was initially approved for the treatment of metastatic colorectal cancer, where its addition to irinotecan-based chemotherapy was shown to improve patient survival [60]. Subsequent approvals have extended its use to renal cell carcinoma, nonsquamous non-small cell lung cancer, and glioblastoma, with supporting evidence from various clinical studies.

In addition to monoclonal antibodies, several tyrosine kinase inhibitors (TKIs) - including sunitinib, sorafenib, and axitinib - have been developed. These agents inhibit multiple angiogenic receptors such as VEGFRs, PDGFRs, and FGFRs, thereby disrupting downstream signaling cascades involved in tumor vascularization.

However, the long-term efficacy of anti-angiogenic therapies is often limited by the development of resistance. Tumors may activate alternative angiogenic pathways involving fibroblast growth factors (FGF) or angiopoietin-2 (Ang2), or adopt compensatory mechanisms such as vessel co-option and immune evasion [29]. These resistance phenomena present a major challenge in sustaining clinical responses over time.

2. Canine hemangiosarcoma

Spontaneous tumors in dogs and cats often exhibit similar angiogenic features to human cancers, making them valuable comparative oncology models.

Hemangiosarcoma (HSA) is an aggressive malignancy of endothelial origin, most commonly affecting the spleen, liver, and right atrium in dogs. This tumor is characterized by extremely high expression of vascular endothelial growth factor A (VEGF-A), along with elevated signaling through VEGFR-2 (also known as KDR) [14]. Histologically, HSA exhibits chaotic and poorly organized vasculature, frequently accompanied by hemorrhage and necrosis.

Experimental studies have demonstrated that canine HSA cells are responsive to VEGF stimulation in vitro, exhibiting enhanced proliferation and angiogenic activity. Furthermore, when implanted in xenograft models, these cells can give rise to highly vascularized tumors that recapitulate key morphological and angiogenic features characteristic of angiosarcoma [46].

3. Canine and feline mammary tumors

Mammary tumors in both dogs and cats share histological and molecular similarities with human breast cancer. In dogs, VEGF expression has been reported to correlate with advanced clinical stage and metastatic potential in certain malignancies, serving as a prognostic biomarker [62]. In cats, histological grading has been identified as a key predictor of prognosis, although fewer studies have evaluated angiogenesis-specific markers such as VEGF in feline mammary carcinoma [78,110]. Notably, feline mammary carcinomas tend to be more biologically aggressive than their canine or human counterparts.

4. Comparative analysis

Human and canine tumors frequently exhibit comparable overexpression of VEGF-A, which plays a central role in promoting angiogenesis. In contrast, the VEGF-C and VEGF-D axis, which is associated with lymphangiogenesis, remains less extensively studied in veterinary oncology. Quantification of VEGF levels using immunohistochemistry and ELISA has been validated in both species; however, these assays currently lack standardized thresholds, limiting their comparability across studies.

The tumor vasculature in both dogs and humans displays similar morphological abnormalities, including increased tortuosity, structural heterogeneity, and detachment of pericytes from endothelial cells. Notably, electron microscopy analyses of canine hemangiosarcoma have revealed immature endothelial junctions, indicative of structurally abnormal tumor vasculature - features that have also been described in highly angiogenic human tumors, such as glioblastoma multiforme [58].

Although anti-angiogenic therapies have not yet been standardized in veterinary oncology, several pilot investigations have explored their potential. Toceranib phosphate [Palladia], a multi-kinase inhibitor targeting VEGFR, PDGFR, and c-kit, has been investigated in canine hemangiosarcoma and other soft tissue sarcomas. However, clinical benefit has been variable, and prospective studies have not consistently demonstrated a survival advantage, underscoring the need for

improved patient selection and combination strategies [38]. In addition, off-label use of agents such as bevacizumab and thalidomide analogs has been attempted; however, their broader application is limited by high costs and insufficient safety data in veterinary patients.

Overall, the use of companion animal tumor models offers significant translational potential for evaluating angiogenesis-targeting agents. These models provide the advantage of studying drug responses in spontaneous tumors within immunocompetent hosts, thereby more accurately reflecting the complexities of clinical oncology.

IV. OCULAR ANGIOGENIC DISEASES

Ocular angiogenesis plays a pivotal role in the pathogenesis of multiple vision-threatening disorders. In both humans and companion animals, aberrant neovascularization in the eye can lead to hemorrhage, exudation, retinal detachment, and eventual blindness. Although human retinal diseases such as diabetic retinopathy [DR] and age-related macular degeneration (AMD) are well-characterized, ocular angiogenic pathologies in dogs and cats are comparatively underresearched, despite shared anatomical and physiological similarities.

1. Diabetic retinopathy

Diabetic retinopathy (DR) is the most prevalent microvascular complication of diabetes mellitus and a leading cause of blindness among working-age adults globally. Chronic hyperglycemia contributes to the pathogenesis of DR by inducing pericyte loss, endothelial dysfunction, and the breakdown of the blood-retina barrier (BRB). These pathological changes promote retinal hypoxia, which in turn triggers the upregulation of pro-angiogenic mediators such as vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1α (HIF-1α). In proliferative diabetic retinopathy (PDR), neovascularization develops on the retinal surface and optic disc, frequently resulting in vitreous hemorrhage and tractional retinal detachment [49]. In diabetic retinopathy, vascular leakage and pericyte loss are closely linked to endothelial barrier failure and inflammatory activation. The author's previous studies demonstrated that STAT3 activation, angiopoietin-2 signaling, interleukin-1β, and microglial activation contribute to pericyte apoptosis, tight junction disruption, and increased vascular permeability in diabetic retinal disease models [40,42,70,104,106,108,109]. These findings are relevant to the broader discussion of angiogenesis-associated vascular remodeling and microvascular instability across species.

2. Age-related macular degeneration

In neovascular or "wet" age-related macular degeneration (AMD), the formation of choroidal neovascularization (CNV) beneath the retinal pigment epithelium is the hallmark pathological feature. This process is driven by overexpression of VEGF in response to oxidative stress, lipid accumulation, and drusen deposition in the macula [80].

The advent of intravitreal anti-VEGF therapies has revolutionized the management of neovascular retinal diseases. Agents such as ranibizumab, aflibercept, and bevacizumab effectively neutralize VEGF-A activity, thereby suppressing pathological neovascularization. In the treatment of neovascular AMD, repeated intravitreal injections - particularly with ranibizumab - have been shown to stabilize or improve visual acuity in a significant proportion of patients [79].

3. Hypertensive retinopathy

Although less prevalent than in humans, companion animals also develop a range of retinal and vascular diseases, many of which involve dysregulation of angiogenic processes. These naturally occurring conditions offer potential comparative insights for translational ophthalmic research.

Systemic hypertension in cats, often secondary to underlying conditions such as renal disease or hyperthyroidism, can result in a range of retinal vascular changes. These include retinal hemorrhages, increased tortuosity of retinal vessels, and serous retinal detachment. Histopathological studies of the feline retina under hypertensive conditions have demonstrated evidence of vascular leakage and retinal lesions consistent with ischemic injury [59,90]. Such features suggest the potential involvement of angiogenic mechanisms, although direct evidence for ischemia-induced upregulation of VEGF in this context is limited [25,59].

4. Progressive retinal atrophy

Progressive retinal atrophy (PRA) encompasses a group of inherited retinal degenerative diseases in dogs, characterized by the progressive loss of rod and cone photoreceptors. Clinically, PRA typically presents as night blindness in its early stages and advances to complete vision loss as photoreceptor degeneration

progresses. Histopathological examination of PRA-affected retinas reveals photoreceptor apoptosis, thinning of the outer nuclear layer, and structural remodeling of the retina. In advanced stages, experimental studies have shown significant upregulation of inflammatory and hypoxia-related genes, consistent with reactive gliosis and metabolic stress responses rather than overt neovascularization. Nevertheless, current literature has not clearly documented secondary neovascularization in canine PRA models, as progressive retinal atrophy is primarily characterized by photoreceptor degeneration and retinal atrophy [74].

5. Comparative ophthalmic angiogenesis

Infectious and immune-mediated diseases, such as feline toxoplasmosis, can induce choroidal inflammation and immune-mediated vasculitis in affected cats. These inflammatory processes are hypothesized to contribute to pathological angiogenesis. However, direct evidence linking these retinal vascular abnormalities to defined angiogenic pathways remains limited, and further studies are needed to clarify these associations [8].

The retinal vascular architecture varies notably between species. Dogs, cats, and humans are generally classified as having holangiotic retinas, in which most of the retina is vascularized. Interspecies differences are more evident in regional specializations [e.g., area centralis/visual streak] and in the distribution and density of retinal vascular plexuses, which may influence the pattern and extent of ischemia-driven vascular remodeling and the detectability of microvascular changes on imaging.

Fluorescein angiography (FA) and optical coherence tomography (OCT) are widely utilized in both human and veterinary ophthalmology to evaluate retinal vascular integrity and morphology. In recent years, OCT-angiography (OCT-A) has gained prominence in human retinal diagnostics by enabling non-invasive visualization of microvascular networks. Although OCT-A is being increasingly explored in veterinary settings, particularly in dogs and cats, its application remains largely experimental and lacks species-specific standardization [66].

Dogs have been employed in experimental models that closely resemble human retinal diseases. For instance, laser-induced choroidal neovascularization (CNV) in dogs replicates key features of neovascular age-related macular degeneration (AMD), while oxygen-induced retinopathy (OIR) models simulate the pathophysiology of diabetic retinopathy (DR). Additionally, feline hypertensive retinopathy demonstrates clinical similarities to human hypertensive retinal changes, including retinal hemorrhages, vascular tortuosity, and ischemia-associated retinal changes. These parallels reinforce the potential of companion animals as translational models for studying angiogenesis-related ocular disorders.

V. INFLAMMATORY AND ISCHEMIC ANGIOGENESIS

Angiogenesis is not only a feature of cancer and retinopathy but also plays a critical role in chronic inflammatory and ischemic diseases. In these contexts, angiogenesis is often dysregulated, resulting in leaky, immature, and disorganized vasculature, which can perpetuate inflammation and tissue damage. The interactions between immune cells, endothelial cells, and inflammatory cytokines such as TNF-α, IL-1β, and IL-6 form a complex regulatory network that governs pathological neovascularization.

1. Rheumatoid arthritis

Synovial angiogenesis is a hallmark of rheumatoid arthritis (RA), playing a central role in the development of pannus tissue, joint erosion, and chronic inflammation. Within the inflamed synovium, macrophages and fibroblasts are activated by pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), which in turn stimulate the production of angiogenic mediators including VEGF, IL-8, and angiopoietins. Notably, the density of microvessels within the synovium has been shown to correlate positively with disease activity and with clinical response to anti-TNF therapies [35,93].

2. Inflammatory bowel disease

In patients with Crohn's disease and ulcerative colitis, increased mucosal vascular density and elevated VEGF expression have been consistently observed. These angiogenic responses are driven in part by hypoxia within the inflamed intestinal tissue and by microbial-derived factors such as lipopolysaccharide (LPS). These stimuli activate hypoxia-inducible factor-1α (HIF-1α), which in turn promotes the expression of VEGF and chemokines such as CXCL8 that further amplify angiogenesis and leukocyte recruitment [10,52,54].

Similar to the human condition, dogs and cats affected by chronic enteropathies display significant mucosal alterations that reflect active angiogenesis and inflammation. These include increased vascular density within the lamina propria, elevated expression of VEGF and interleukin-6 (IL-6) in intestinal mucosa, and structural disruption of the epithelial barrier. The enhanced vascularity and immune cell infiltration in these animals are closely associated with disease activity, suggesting mechanistic parallels with human IBD [63].

3. Ischemic diseases

Angiogenesis following ischemic injury plays a critical role in restoring tissue perfusion in both ischemic heart disease and stroke. However, the resulting neovascularization is often insufficient or structurally abnormal. The angiogenic response in ischemic tissues is largely orchestrated by VEGF-A, angiopoietin-1, and platelet-derived growth factor (PDGF), whose expression is modulated by local hypoxia and oxidative stress. These mediators contribute to the remodeling of the microvascular network in an effort to restore oxygen and nutrient delivery to affected tissues [19,22,57].

4. Veterinary inflammatory disorders

Feline chronic gingivostomatitis (FCGS) is a severe, idiopathic oral inflammatory disease marked by extensive lymphoplasmacytic infiltration, fibrosis, and prominent angiogenic activity. Although the precise etiopathogenesis remains unclear, angiogenic mediators such as vascular endothelial growth factor (VEGF) and transforming growth factor beta 1 (TGF-β1) are suspected to play roles in aberrant vascular remodeling observed in inflamed gingival tissues. However, quantitative data on these factors in feline oral lesions remain limited [88].

Angiogenesis is a central component of wound healing, particularly during the formation of granulation tissue. In both dogs and cats, the normal course of wound repair may be modified by systemic or local factors such as secondary infections, immunosuppressive treatments, or metabolic diseases. These influences can impair or alter angiogenic responses, potentially delaying tissue regeneration and complicating clinical management.

Tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are traditionally recognized as key pro-inflammatory cytokines, but they also exert potent pro-angiogenic effects through downstream activation of signaling pathways such as nuclear factor kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT3). In both humans and companion animals, chronic inflammation promotes a sustained loop of cytokine release, endothelial activation, and neovascularization. Notably, increased expression of vascular endothelial growth factor (VEGF) together with elevated levels of inflammatory cytokines has been well documented in human rheumatoid arthritis (RA), where pro-inflammatory cytokines such as IL-17 and IL-18 directly promote VEGF production in synovial fibroblasts. In feline chronic gingivostomatitis (FCGS), severe immune cell infiltration and dysregulated inflammatory cytokine responses are prominent features, suggesting mechanistic parallels between these diseases driven by chronic inflammation and cytokine-mediated angiogenic pathways [13,36,82,97].

Hypoxia is a fundamental stimulus for angiogenesis in both ischemic and inflammatory contexts. The stabilization of hypoxia-inducible factor-1α (HIF-1α) is a key event that regulates the transcription of angiogenic mediators, including VEGF. However, the kinetics of HIF-1α stabilization and its downstream effects can vary between species, influencing the magnitude and duration of the angiogenic response. In dogs, robust HIF-1α expression has been demonstrated in ischemic myocardium [89], and similar hypoxia-associated upregulation has been suggested in the colonic mucosa under inflammatory or ischemic conditions. These findings mirror patterns seen in human diseases such as inflammatory bowel disease (IBD) and ischemic stroke, highlighting the conserved role of hypoxia signaling across species.

Canine models of IBD are increasingly used to evaluate the efficacy of biologic agents targeting cytokine pathways such as IL-12/IL-23, as well as experimental anti-VEGF therapies. Similarly, FCGS represents a naturally occurring model of chronic oral mucosal inflammation, providing a comparative platform relevant to human conditions such as lichen planus and recurrent oral ulcers. These veterinary models offer valuable insights into disease mechanisms and therapeutic interventions, supporting their utility in translational research.

VI. ANGIOGENESIS-RELATED BIOMARKERS AND DIAGNOSTICS

A comparative summary of key angiogenesis-related biomarkers across humans, dogs, and cats is provided in Table 2. This includes molecules such as VEGF-A, Angiopoietins, soluble VEGF receptors, and HIF-1α, highlighting species-specific expression patterns, diagnostic relevance, and their prognostic or therapeutic significance in oncology, ophthalmology, and cardiovascular diseases. These biomarkers are clinically useful in both human and veterinary contexts.

The identification and quantification of angiogenesis-related biomarkers provide valuable diagnostic, prognostic, and therapeutic insights in a wide range of diseases. While angiogenic biomarkers are well-established in human medicine for oncology, ophthalmology, and cardiovascular conditions, their application in veterinary medicine is still emerging. A comparative understanding of these biomarkers across species enhances translational research and supports the development of targeted therapies.

VEGF-A is the most extensively studied isoform and serves as a direct marker of active angiogenesis. Circulating VEGF levels are known to be elevated in various human diseases, including colorectal, breast, and renal cancers, as well as diabetic retinopathy and age-related macular degeneration (AMD). Similar elevations have been observed in canine conditions such as hemangiosarcoma and mammary carcinoma. In both humans and dogs, plasma and serum VEGF concentrations have been shown to correlate with tumor burden and metastatic potential in canine cancers, and with disease progression and clinical prognosis in human malignancies [15,43,44,83].

Angiopoietin-1 (Ang1) plays a critical role in maintaining vascular integrity through activation of the Tie2 receptor. In contrast, Angiopoietin-2 (Ang2) disrupts endothelial junctions and promotes vascular sprouting, particularly in the presence of VEGF. An increased Ang2/Ang1 ratio has been associated with several human pathological conditions, including sepsis, cancer, and retinal neovascularization. In veterinary medicine, an imbalance favoring Ang2 over Ang1 has been reported in dogs with inflammatory diseases and neoplasia [48,92].

Soluble forms of VEGF receptors, including sVEGFR-1 and sVEGFR-2, function as decoy receptors that bind circulating VEGF and modulate its bioavailability. Alterations in the levels of soluble angiogenic receptors have been documented in various human conditions such as preeclampsia and diabetic retinopathy, while changes in angiogenic signaling pathways, including circulating VEGF levels, have been reported in experimentally induced or spontaneous tumors in dogs [37,61,100].

HIF-1α is a master transcriptional regulator of angiogenesis under hypoxic conditions. Elevated expression of HIF-1α reflects tissue hypoxia and has been closely linked to pathological angiogenesis in human diseases such as ischemic stroke and solid tumors. Similarly, activation of hypoxia-responsive angiogenic pathways has been documented in dogs with myocardial ischemia, as evidenced by increased expression of downstream targets such as VEGF, consistent with the established role of HIF-1α in myocardial ischemia models [41,113].

Immunohistochemistry remains the gold standard for assessing the local expression of angiogenesis-related markers such as VEGF, HIF-1α, CD31 (PECAM-1), and von Willebrand factor (vWF). This technique is extensively utilized in both human and veterinary pathology for tumor grading through microvessel density (MVD) quantification using CD31, as well as for evaluating angiogenesis associated with inflammation. The method has been validated for use in dogs and cats, provided that species-specific or cross-reactive antibodies are employed [31,102].

ELISA is a widely used quantitative technique for detecting circulating levels of angiogenic factors, including VEGF, Angiopoietin-2 (Ang2), and soluble VEGF receptors (sVEGFR) in serum or plasma. Although most commercial ELISA kits are designed for human targets, many exhibit cross-reactivity with canine and feline proteins. Nevertheless, species-specific validation remains essential to ensure analytical accuracy and biological relevance in veterinary applications [31,73,102].

Molecular approaches such as quantitative PCR (qPCR) and RNA sequencing (RNA-Seq) are commonly employed to measure the expression of genes associated with angiogenesis, including VEGF, HIF1A, and ANGPT1/2. These methods are particularly useful in research settings involving tumor biopsies, inflamed tissues, or retinal specimens, providing valuable insights into transcriptional regulation and species-specific expression patterns.

Table 2. Angiogenesis-related biomarkers in humans, dogs, and cats.

Biomarker	Human	Dog	Cat
Circulating VEGF-A	Elevated in cancers, diabetic retinopathy, AMD. Quantified via ELISA or IHC; correlated with disease severity.	Detected in canine mammary tumors and hemangiosarcoma; serum VEGF correlated with prognosis.	Reported/implicated in feline mammary carcinoma; evidence in hypertensive retinopathy is limited and largely indirect; circulating data are sparse.
HIF-1α	Tissue-level marker for hypoxia and angiogenic activation; predictive in cancer and ischemic injury.	Observed in ischemic myocardial and tumor samples; upstream regulator of VEGF.	Immunohistochemically identified in mammary carcinoma with prognostic implications.
Endothelial activation markers (e.g., HA, PAI-1)	Used in vascular inflammation; associated with tumor aggressiveness.	Elevated in systemic inflammation and sepsis; correlated with disease progression.	No significant data available yet.
Circulating endothelial cells (CEC)	Used in clinical oncology; associated with angiogenic activity and treatment response.	Reported to be altered in dogs with cancer; potential biomarker requiring further standardization and validation.	Unstudied or insufficient data.

Doppler ultrasound and contrast-enhanced ultrasound (CEUS) are valuable imaging modalities used to asstable ess tissue perfusion and vascular architecture, particularly in tumors and inflamed organs. CEUS has been validated in veterinary medicine, especially for evaluating hepatic neoplasia and intestinal inflammation in dogs, providing real-time insights into functional vascular changes [3,56].

OCT and OCT-A are non-invasive imaging techniques that allow high-resolution visualization of retinal and choroidal microvasculature. While widely utilized in human ophthalmology for diagnosing diabetic retinopathy and age-related macular degeneration (AMD), these modalities are increasingly being adapted for veterinary use. Applications include the assessment of hypertensive retinopathy in dogs and cats, as well as experimental animal models of retinal diseases such as age-related macular degeneration and diabetic retinopathy [47,50,68,72,96].

Although many angiogenic pathways are conserved across species, allowing for partial application of human diagnostic reagents and imaging protocols in veterinary contexts, several limitations persist. These include the lack of veterinary-validated reagents such as antibodies, variability in the reference ranges for circulating angiogenic biomarkers, and inconsistent sensitivity and resolution of imaging tools in small animal species. Despite these challenges, companion animals with naturally occurring diseases serve as valuable models for translational research, particularly in the fields of oncology and ocular angiogenesis [27,51,76,111].

VII. ANTI-ANGIOGENIC AND PRO-ANGIOGENIC THERAPEUTICS

A comparative overview of anti- and pro-angiogenic therapeutic strategies used in humans, dogs, and cats is summarized in Table 3. This includes approved clinical agents, off-label applications in veterinary medicine, and investigational therapies with translational potential.

The inhibition of angiogenesis has become an essential component of modern oncology. One of the most widely used agents is bevacizumab (Avastin), a humanized monoclonal antibody that targets VEGF-A. It is approved for the treatment of several malignancies, including colorectal cancer, renal cell carcinoma, glioblastoma, and non-small cell lung cancer [26]. In addition to monoclonal antibodies,

several tyrosine kinase inhibitors (TKIs), such as sunitinib, sorafenib, and axitinib, have been developed to block angiogenic pathways involving VEGFR, PDGFR, and FGFR [28,39]. These anti-angiogenic agents contribute to reduced tumor vascularization, normalization of aberrant blood vessels, and enhancement of chemotherapeutic efficacy. However, treatment resistance remains a major challenge and may arise through mechanisms such as hypoxia-induced adaptation, activation of alternative angiogenic pathways (e.g., FGF, Ang2), or tumor cell-driven vascular mimicry [29,99].

In the field of ophthalmology, anti-VEGF therapies have revolutionized the management of neovascular retinal diseases. Intravitreal injection of anti-VEGF agents such as ranibizumab, aflibercept, and off-label bevacizumab has become the standard of care for conditions including neovascular age-related macular degeneration (AMD), diabetic retinopathy, and retinal vein occlusion [9,94]. These agents effectively inhibit pathological neovascularization, reduce macular edema, and often stabilize vision and, in many patients, improve visual outcomes.

Therapeutic angiogenesis is employed in conditions characterized by ischemia, such as critical limb ischemia, coronary artery disease, and post-stroke recovery. Pro-angiogenic approaches include the use of VEGF and fibroblast growth factor (FGF) gene therapy, protein delivery of Angiopoietin-1 (Ang1), and the pharmacological stabilization of hypoxia-inducible factor-1α (HIF-1α) using agents such as roxadustat. These interventions aim to enhance endogenous vascular growth and improve perfusion in ischemic tissues [20].

Although no angiogenic modulators have received formal regulatory approval specifically for angiogenesis-targeted therapy in veterinary medicine, several off-label and investigational applications have been reported in clinical and experimental veterinary settings.

Toceranib phosphate (Palladia), a multi-targeted tyrosine kinase inhibitor that acts on VEGFR, PDGFR, and c-kit, has been approved for the treatment of canine mast cell tumors. Beyond its approved indication, toceranib has been explored for its anti-angiogenic potential in other canine malignancies, including hemangiosarcoma and anal sac adenocarcinoma [4,30]. Thalidomide and its analogs exhibit anti-angiogenic and immunomodulatory effects and have been extensively studied in human oncology, with only limited exploratory reports in veterinary medicine, including dogs [21,65,77]. Furthermore, bevacizumab, a monoclonal antibody against VEGF-A, has shown experimental promise in veterinary oncology and ophthalmology. However, its widespread use in animals is limited by factors such as high cost and potential immunogenicity [64,86].

While pro-angiogenic therapies remain limited in veterinary clinical practice, several experimental approaches have been explored. These include the topical application of VEGF or basic fibroblast growth factor (bFGF) to promote healing in corneal ulcers and dermal wounds. In addition, hyperbaric oxygen therapy (HBOT) has been investigated as a non-pharmacological approach to promote angiogenesis and improve perfusion in ischemic or poorly vascularized tissues [55].

Companion animals, particularly dogs with spontaneous tumors such as osteosarcoma and hemangiosarcoma (HSA), offer valuable translational insights due to their naturally occurring tumor microenvironments and angiogenic signaling pathways that closely mirror those observed in human cancers. These similarities extend to vascular remodeling, hypoxia responses, and VEGF-driven neovascularization. Additionally, feline hypertensive retinopathy has been suggested as a clinically relevant condition for investigating retinal vascular pathology and therapeutic responses, with potential implications for studies of ocular angiogenic modulation [11,16].

The concept of One Health highlights the integrative potential of comparative angiogenesis research in bridging veterinary and human medicine. Dogs and cats serve as important intermediary models due to their shared molecular mechanisms and therapeutic targets, particularly within VEGF-related pathways. This cross-species similarity enables their use in preclinical screening of anti-VEGF agents, evaluation of drug toxicity and efficacy, and pharmacokinetic bridging studies that inform human drug development. Such translational applications strengthen the relevance of veterinary models in advancing angiogenesis-targeted therapeutics across species boundaries.

Table 3. Comparative summary of anti- and pro-angiogenic therapeutics.

Therapeutic Strategy	Human	Dog	Cat
Anti-VEGF therapy (e.g., Bevacizumab)	Common in oncology and ophthalmology; blocks VEGF to suppress angiogenesis.	Off-label use in tumors; Palladia (Toceranib) inhibits VEGFR among others.	Not routinely used clinically; evidence is limited and use is constrained by cost, immunogenicity concerns, and lack of veterinary-approved biologics.
Tyrosine kinase inhibitors (TKIs)	Sunitinib and sorafenib target VEGFR and PDGFR in cancers.	Toceranib phosphate approved for mast cell tumors; cross-reactivity with angiogenic targets.	No approved agents; data unavailable.
Pro-angiogenic gene therapy	Experimental use of VEGF/FGF gene transfer or HIF stabilization in ischemic disease.	Limited veterinary trials for wound healing and corneal repair.	No known applications.
Liquid biopsy markers	Emerging tools include circulating VEGF, CECs, and angiogenic miRNAs.	Emerging veterinary studies include circulating VEGF/Ang2, soluble VEGF receptors, circulating endothelial cells, and angiogenesis-related microRNAs; however, standardization and clinical validation remain limited.	Little or no data available.

VIII. CHALLENGES AND FUTURE DIRECTIONS

Although substantial progress has been made in elucidating the mechanisms of angiogenesis in human health and disease, similar advancements in veterinary medicine, particularly concerning companion animals, remain relatively underdeveloped. Considering the shared pathophysiological pathways underlying angiogenesis and the need to overcome current limitations in anti-angiogenic therapies, a focused and systematic approach is required to realize the full potential of comparative angiogenesis research [29,39].

One of the primary obstacles is the limited availability of species-specific data. Much of the existing molecular knowledge regarding angiogenesis derives from murine models and human clinical studies, while detailed gene expression profiles, receptor polymorphism data, and cytokine signaling pathways in dogs and cats remain sparse. This scarcity hampers the development of targeted therapeutics, complicates biomarker validation, and restricts the accuracy of mechanistic comparisons across species.

Another challenge lies in the lack of standardized diagnostic protocols for veterinary use. Most clinical settings lack validated diagnostic tools such as ELISA kits, immunohistochemical antibodies, and imaging modalities specifically tailored to canine and feline patients. Although human-derived reagents are often employed under the assumption of cross-reactivity, such assumptions are not consistently supported by formal validation studies, leading to variability and uncertainty in diagnostic results [5,101].

In terms of treatment, the therapeutic landscape for veterinary anti-angiogenic interventions is extremely limited. Aside from toceranib phosphate, which is approved for the treatment of canine mast cell tumors, no anti-angiogenic agents have received regulatory approval specifically for angiogenesis-targeted veterinary applications [4,69]. Off-label use of human biologics, such as bevacizumab, is further constrained by issues related to high cost, immunogenicity, and legal or regulatory limitations.

Several practical limitations hinder progress in clinical angiogenesis research within the veterinary field. Chief among these is the small sample size encountered in most veterinary clinics, which limits statistical power and generalizability [33]. Moreover, veterinary clinical trials receive significantly less governmental and industrial funding compared to human medical research.

Ethical and logistical challenges further complicate research efforts. Invasive procedures, including tumor biopsies and collection of ocular fluids, are often not feasible in privately owned pets due to welfare concerns and owner reluctance. In addition, the absence of centralized biobanks and standardized tissue repositories in veterinary medicine limits access to well-characterized biological samples for large-scale studies.

Future research efforts should prioritize the development of species-specific reagents. This includes the generation of canine and feline-specific antibodies, ELISA kits, and multiplex cytokine panels. Expansion of RNA sequencing and proteomic databases for companion animals is also necessary to build a comprehensive map of angiogenic signaling profiles.

The integration of advanced imaging modalities into veterinary diagnostics represents another promising avenue. Techniques such as optical coherence tomography angiography (OCT-A), contrast-enhanced ultrasound (CEUS), and magnetic resonance imaging with angiographic contrast agents could significantly improve the *in vivo* assessment of angiogenesis [17,45,53]. The development of portable and cost-effective imaging platforms may further facilitate their use in clinical practice.

In addition, systems biology approaches integrating transcriptomic and network-based analyses provide powerful tools for unraveling the complexity of angiogenesis in inflamed, ischemic, or neoplastic tissues [112]. Cross-species comparisons enabled by ortholog mapping can help identify conserved therapeutic targets and inform translational applications.

The use of dogs and cats as spontaneous disease models holds considerable promise for translational research. Compared to experimentally induced conditions in rodents, naturally occurring diseases in companion animals more accurately reflect the complex pathophysiology of human disorders. These models offer unique advantages, including intact immune systems, natural disease progression, and real-world clinical variability in treatment response.

To capitalize on these strengths, interdisciplinary collaboration is essential. Veterinarians, physicians, immunologists, and computational scientists must work together to establish integrated research frameworks [23]. Creating One Health consortia focused on angiogenesis could accelerate the identification of shared biomarkers, cross-species therapeutic strategies, and predictive algorithms for treatment response [91].

Collectively, these challenges and opportunities underscore the need for increased investment, standardization, and interdisciplinary cooperation to bridge the gap between veterinary and human angiogenesis research.

IX. CONCLUSION

Angiogenesis is a fundamental biological process that plays pivotal roles in both physiological and pathological contexts. In human medicine, angiogenesis has been extensively studied in diseases such as cancer, retinopathy, and chronic inflammatory conditions, leading to the development of effective diagnostic tools and targeted therapies. In contrast, angiogenesis research in veterinary medicine - particularly in companion animals like dogs and cats - has remained relatively underdeveloped, despite increasing recognition of its clinical relevance.

Comparative analysis reveals substantial similarities in the molecular pathways of angiogenesis across species, particularly involving key mediators such as VEGF, FGF, Angiopoietins, and matrix metalloproteinases. These conserved pathways support the idea that insights from one species can inform understanding and treatment in another. However, species-specific differences in gene expression, vascular architecture, and immune responses also highlight the need for dedicated veterinary studies, rather than simple extrapolation from human models.

In oncology, ocular disease, and inflammatory conditions, the parallels between human and veterinary angiogenic mechanisms are striking. Yet, challenges such as the lack of validated diagnostic reagents, limited clinical trial infrastructure, and restricted access to anti-angiogenic agents continue to hinder translational progress in veterinary practice. The shortage of species-specific molecular data and imaging tools further limits the precision of veterinary diagnostics and therapeutics.

To harness the full potential of comparative angiogenesis research, it is imperative to overcome these scientific and systemic limitations. Investment in veterinary-specific tools, the development of cross-species omics databases, and the implementation of collaborative clinical trials will be essential. Moreover, the integration of advanced imaging modalities and systems biology approaches can elevate the resolution at which angiogenic processes are studied in companion animals.

The One Health framework provides a powerful rationale for aligning human and veterinary angiogenesis research. Spontaneous diseases in dogs and cats offer unique opportunities for modeling complex, chronic, and immune-influenced angiogenic pathologies. Through coordinated efforts across disciplines - including veterinary medicine, human clinical research, pharmacology, and bioinformatics - comparative studies can accelerate the discovery of novel biomarkers, therapeutic targets, and predictive algorithms.

In conclusion, while significant gaps remain, the convergence of comparative biology and translational medicine opens new horizons for angiogenesis research. Bridging these gaps will not only improve veterinary care but also enrich human medical knowledge, advancing a truly integrative, cross-species approach to tackling angiogenesis-related diseases.

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