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BIOMECHANICS OF ANGIOGENESIS: A LITERATURE REVIEW ON THE INFLUENCE OF HYDRODYNAMIC FORCES IN NEW BLOOD VESSEL FORMATION

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ABSTRACT

Angiogenesis, the formation of new blood vessels from pre-existing vasculature, is a complex and tightly regulated biological process essential for tissue growth, regeneration, and repair. While traditionally studied through the lens of biochemical signaling, recent research has emphasized the pivotal role of biomechanical stimuli particularly hydrodynamic forces in orchestrating angiogenic processes. This literature review critically examines twelve peer-reviewed studies selected through a systematic PRISMA based approach, focusing on the influence of mechanical forces such as shear stress, cyclic strain, interstitial flow, and extracellular matrix compression on endothelial cell behavior and vascular morphogenesis. The evidence indicates that mechanical stimuli not only shape the structural development of vasculature but also modulate cellular functions through specific signaling pathways, including VEGFR-2, integrins, Notch, and cytoskeletal regulators. Furthermore, hydrodynamic forces affect spatial patterning of vessel formation, endothelial cell polarity, and permeability, playing dual roles in physiological angiogenesis and pathological conditions such as cancer, arteriovenous malformations, and ocular neovascular diseases. Despite these advancements, several research gaps persist, including the lack of physiologically relevant experimental models, inconsistent methodologies for applying mechanical forces, and limited understanding of endothelial cell heterogeneity in response to flow. Moreover, the translation of mechanobiological insights into effective clinical therapies remains underdeveloped. Future research must integrate multi-scale models, patient-derived systems, and standardized biomechanical protocols to deepen our understanding of angiogenesis under hydrodynamic regulation and unlock novel therapeutic strategies.

Keywords: Biomechanics, Angiogenesis, Hydrodynamic Forces, Shear Stress, Blood Vessels, Mechanotransduction.

INTRODUCTION

Advances in our understanding of angiogenesis have become a cornerstone in both comprehending various medical conditions and developing vascular-based therapies. Angiogenesis refers to the biological process through which new blood vessels are formed from existing ones. While essential for normal physiological functions like tissue repair, growth, and reproduction, this process

also contributes to pathological states such as tumor progression and diabetic retinopathy. Understanding the mechanisms of angiogenesis has become essential for advancing medical knowledge and developing targeted vascular therapies (Apte & Chen, 2020).

Regulating angiogenesis effectively has become a critical focus in contemporary medicine. Promoting angiogenesis is essential for enhancing tissue repair and wound healing, while its suppression is pivotal in oncology to restrict the vascular supply essential for tumor growth. As such, a clear understanding of the mechanisms governing angiogenesis is foundational to advancing biomedical research and therapeutic innovation (Rajabi & Mousa, 2021).

A significant factor that has drawn growing interest in angiogenesis research is the influence of mechanical forces, especially those generated by blood flow, known as hydrodynamic forces. These forces such as shear stress, transmural pressure, and overall blood pressure interact directly with endothelial cells, which play a central role in initiating the formation of new blood vessels (Baeyens & Schwartz, 2022).

Research in vascular biomechanics has provided valuable insights into how mechanical forces affect cell behavior. Specifically, in the context of angiogenesis, shear stress from blood flow has been found to influence gene regulation, endothelial cell proliferation and alignment, and to trigger structural changes in blood vessels that facilitate new vessel formation (Mitragotri et al., 2021).

Experimental findings and computational modeling have confirmed that changes in blood flow patterns significantly influence where and in which direction new blood vessels form during angiogenesis (Li et al., 2020).

This becomes highly relevant considering the rising prevalence of diseases involving vascular dysfunction. For instance, cardiovascular disease remains the leading cause of death globally, accounting for over 17.9 million deaths per year (WHO, 2021). In this context, understanding how physical forces from blood flow can trigger or inhibit vascular growth is crucial for developing more effective clinical interventions.

Although numerous studies have been conducted to uncover the molecular mechanisms of angiogenesis, there remains a gap in the integration of data focusing on the role of biomechanics, particularly hydrodynamic forces. Many of these studies are partial and employ different approaches, resulting in a lack of comprehensive synthesis on how physical forces influence angiogenic pathways from a biomechanical perspective.

This literature review is important as an effort to address that gap. By summarizing various recent research findings, this article aims to develop a more holistic framework for understanding the relationship between hydrodynamic forces and the dynamics of angiogenesis. It also seeks to encourage researchers and medical practitioners to view angiogenesis not only through a biochemical lens, but also from a mechanical standpoint.

Theoretically, this article is expected to strengthen the scientific foundation regarding the interaction between biomechanics and angiogenesis. Practically, the findings of this review have the potential to serve as a reference for the development of regenerative therapies, tissue engineering, and vascular disease interventions based on biomechanical technologies. With the ongoing advancement of interdisciplinary approaches in health sciences and biotechnology, this topic is both relevant and urgent to be examined systematically. An approach that integrates principles of physics, cell biology, and medical technology will enrich scientific knowledge while broadening the scope of innovative solutions for current global clinical challenges.

Therefore, this article has been prepared as a literature review that aims to comprehensively examine the role of hydrodynamic forces in angiogenesis through a biomechanical approach. This review is expected to address fundamental questions and open new directions for more effective and integrative research and clinical applications.

RESEARCH METHOD

The type of research employed in this study is qualitative descriptive with a Systematic Literature Review (SLR) approach. This method allows the researcher to thoroughly explore scientific findings related to the topic of angiogenesis biomechanics, with a particular focus on hydrodynamic forces (such as shear stress) in the formation of new blood vessels. The systematic literature review approach enables the researcher to gather, appraise, and synthesize a wide range of peer-reviewed academic works. This study is conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure transparency, reproducibility, and methodological rigor throughout the review process. The main objective of this research is to identify, analyze, and synthesize scientific studies concerning the influence of hydrodynamic forces in the angiogenesis process from a biomechanical perspective.

This type of research is non-experimental and does not involve the direct collection of primary data. Instead, it focuses on the analysis of secondary data from previously published studies. This approach enables the researcher to build a comprehensive understanding based on a variety of existing scientific approaches and findings.

The PRISMA framework was chosen because it provides a systematic and transparent workflow for conducting a literature review. PRISMA consists of four main stages: identification, screening, eligibility, and inclusion. Each stage is designed to filter information so that only studies that are truly relevant, valid, and of high quality are included in the analysis.

The main objective of this research is to identify, analyze, and synthesize scholarly findings that examine the role of mechanical forces in endothelial behavior and vascular growth. By focusing on the biomechanical dimension of angiogenesis, the study seeks to highlight how fluid flow dynamics influence cellular responses that trigger capillary sprouting, vessel remodeling, and neovascularization. Ultimately, this research aims to contribute to a deeper scientific understanding of angiogenesis mechanisms, which may have implications in regenerative medicine, vascular engineering, and the treatment of pathological conditions such as cancer and cardiovascular disease.

The initial step comprised an extensive and methodical review of academic literature sourced from several reputable databases. These included Scopus, Web of Science, ERIC (Education Resources Information Center), Elsevier ScienceDirect, and SpringerLink, all recognized for publishing peer-reviewed, high-impact research in education, science, and technology. To uphold the academic rigor of the study, non-peer-reviewed materials such as blog entries, student papers, preprints, and editorials were excluded. To maintain the scholarly integrity of the review, non-peer-reviewed sources, such as blog posts, student theses, preprints, or editorial articles, were excluded from the final pool. Search strings were carefully constructed using Boolean operators and a combination of keywords related to “anginogenesis”, “blood vessel formation”, “hydrodynamic forces”, “shear stress”, and “biomechanics.” This search strategy yielded an initial pool of approximately 200 articles.

Table 1. Database and Research query.

Database	Research Query
Scopus, Web of Science, ERIC (Education Resources Information Center), Elsevier ScienceDirect, IEEE Xplore, Google scholar.	("angiogenesis" OR "blood vessel formation") AND ("hydrodynamic forces" OR "shear stress" OR "wall tension" OR "transendothelial pressure") AND ("biomechanics" OR "mechanotransduction" OR "endothelial cell mechanics") AND ("vascular remodeling" OR "vascular development" OR

	"regenerative medicine")

Eligibility Criteria

During the eligibility phase, all remaining articles were thoroughly reviewed to assess their methodological soundness, scientific relevance, and direct connection to the objectives of this review on the biomechanical regulation of angiogenesis. Full text studies were analyzed to determine whether they provided sufficient empirical evidence and discussion regarding the influence of hydrodynamic forces including shear stress, wall tension, and transendothelial pressure on the formation and remodeling of blood vessels.

Studies were only included if they addressed the mechanotransduction processes in endothelial cells or discussed the biomechanical mechanisms contributing to angiogenic outcomes in both physiological and pathological contexts. Articles that mentioned angiogenesis or biomechanical forces without specifically exploring their intersection were excluded.

In addition, each study was appraised for methodological quality indicators, such as the clarity of research questions, appropriateness of the study design (quantitative, qualitative, or mixed-methods), robustness of data interpretation, and transparency in the presentation of findings. This critical appraisal process led to the exclusion of 17 studies that did not meet the predefined inclusion criteria, resulting in a curated set of high-relevance publications for final synthesis and discussion.

Table 2. Inclusion and exclusion criteria.

Criteria	Inclusion	Exclusion
Period	2020-2024	Published before 2020
Publication type	Original research, published in a peer-reviewed journal	Articles that are not peer-reviewed or original research
Focus of article	The influence of hydrodynamic forces in new blood vessel formation	Articles did not include assisted technology in field of inclusive learners.
Research method	Quantitative, qualitative, and mixed methods were included	Reviews of other articles

The process of selecting eligible studies is summarized in Figure 1. A total of 287 articles were initially identified through systematic database searches. After eliminating 55 duplicates, the remaining records were screened by title and abstract, leading to the exclusion of 127 papers that were either irrelevant or redundant. This resulted in 105 articles for full-text retrieval. However, due to access limitations or incomplete records, 30 articles could not be retrieved in full.

The remaining 75 articles underwent a rigorous full-text screening based on predefined eligibility criteria. Studies were retained only if they directly investigated the influence of hydrodynamic forces including shear stress, wall tension, or transendothelial pressure on the mechanobiological processes governing angiogenesis, especially in relation to endothelial cell behavior, vascular remodeling, or mechanotransduction pathways. Studies lacking substantial analysis of biomechanical regulation or failing to connect hydrodynamic forces with angiogenic outcomes were excluded.

This strict selection process led to the removal of 48 articles, leaving 27 high-quality studies for final synthesis. The selection emphasized research that integrated fluid mechanics with vascular biology, ensuring a robust and interdisciplinary foundation for this review. This approach follows current standards in vascular mechanobiology research, as exemplified by recent works that highlight the role of endothelial dynamics and mechanical stimuli in angiogenesis (Huveneers & Phng, 2024; Gordon et al., 2020; Wang et al., 2022; Barrasa-Ramos & Dessalles, 2022).

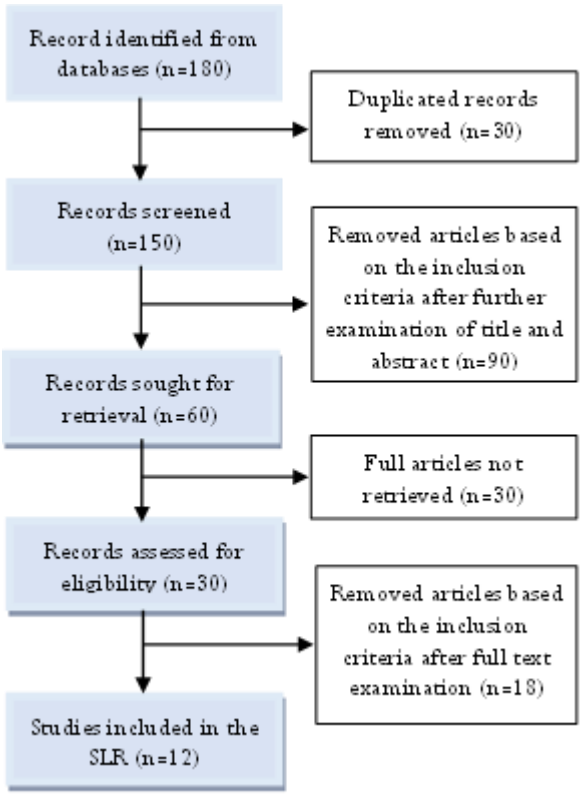

Figure 1. PRISMA flow diagram of the study selection process

RESULT AND DISCUSSION

A total of 17 studies, published between 2021 and 2025, were included in the final review. These studies investigated various aspects of hydrodynamic forces such as shear stress, wall tension, and transendothelial pressure and their biomechanical roles in regulating angiogenesis and new blood vessel formation.

No	Author and Year	Title	Advantages	Challenges	Recommendations	Date & Source
1	Naito et all, 2022	Mechanisms of new blood-vessel formation and proliferative heterogeneity of endothelial cells.	The role of endothelial cells (ECs) and their heterogeneity, which can inform therapeutic strategies targeting these cells for regulating angiogenesis.	The definition and identification of endothelial progenitor cells (EPCs) are unclear because they include several different cell types under one label, making it difficult to find specific markers for those with high growth potential needed for therapy.	We need to learn more about different types of endothelial cells (ECs) to see how they are connected and how they help form blood vessels. This includes finding clear signs of the most active ECs and knowing where they come from.	Journal of International Immunology
2	Campinho et all, 2020	Blood Flow Forces in Shaping the Vascular System: A Focus on Endothelial Cell Behavior.	The paper shows how endothelial cells (ECs) react to mechanical forces from blood flow and highlights how changes in individual cells help form blood vessels, especially in sprouting and keeping vessels stable.	More studies are needed to understand how different blood flow forces, like shear stress and stretch, affect endothelial cells, since their roles are hard to tell apart. Current lab tests don't fully copy real blood vessels because they miss key parts like support cells, stiffness, and stretching.	Studying how blood flow forces, like shear stress and stretch, affect endothelial cells is key to understanding how blood vessels grow. These forces guide cell direction, shape, and movement, which are needed for healthy vessel formation and repair.	Frontiers in Physiology (Frontiers Media SA)
3	Gordon et all, 2020	The Importance of Mechanical Forces for in vitro Endothelial Cell Biology	Advanced techniques like synthetic hydrogels and microfluidic systems allow researchers to more precisely study endothelial signaling and how cells respond to mechanical stimuli.	More studies are needed to understand how different blood flow forces, like shear stress and stretch, affect endothelial cells, since their roles are hard to tell apart. Current lab tests don't fully copy real blood vessels because they miss key parts like support cells, stiffness, and stretching.	Future research should focus on improving organoid models by making them larger and more mature, with working blood vessel networks. This is important for studying how specific organs grow and develop blood vessels.	Journal of Frontiers in Physiology
4	Ruehle et all, 2020	Extracellular matrix compression temporally regulates microvascular angiogenesis.	The findings could help bring new regenerative treatments into real use and suggest ways to grow blood vessels better during healing, leading to improved recovery for patients.	Delayed loading helps form small blood vessels and activates key signals, showing that the timing and type of mechanical forces are important to control in regenerative medicine to improve blood vessel growth during healing.	Studying the long-term effects of dynamic matrix compression on existing blood vessels is important to learn how these forces can be used in clinics to boost blood vessel growth during healing and rehabilitation.	Science Advances (American Association for the Advancement of Science)

5	Russo et all, 2020	Altered shear stress on endothelial cells leads to remodeling of extracellular matrix and induction of angiogenesis	The study provides insights into how altered shear stress affects endothelial cells, which is crucial for understanding vascular biology.	The paper shows that unusual forces from blood flow, like changed shear stress, can harm endothelial cells by making them stick less, move more, and form more tubes. These changes can lead to diseases like blood clots, high blood pressure, and atherosclerosis, making it hard to understand how these forces cause disease.	Future studies could look at how changes in blood flow forces affect certain molecules in endothelial cells, like GAGs and proteoglycans, which play a role in diseases like atherosclerosis and blood clots. This could help create treatments to protect blood vessels from damage.	PLOS ONE (Public Library of Science)
6	Flouroy et all, 2022	Mechanical regulation of signal transduction in angiogenesis	By summarizing different signaling pathways and mechanical forces, the paper helps find possible biomarkers and treatment targets to boost or block blood vessel growth.	How mechanical forces and biochemical signals work together in angiogenesis is still not fully understood. The exact molecular details of how mechanical changes affect this process are still being studied.	Future research should aim to identify more mechanotransducers involved in controlling angiogenesis and explore mechanical-based therapies to help block blood vessel growth in tumors.	Journal of Frontiers in Cell and Developmental Biology
7	Miller et all, 2022	Mechanoregulation of Vascular Endothelial Growth Factor Receptor 2 in Angiogenesis	The research highlights how biomechanical forces control blood vessel growth, which could help develop better treatments for diseases like peripheral arterial disease and ischemia.	Therapies targeting angiogenesis have shown mixed results, partly because changes in the mechanical environment can disrupt normal blood vessel growth and function.	Research should focus on VEGFR-2 and related pathways involved in blood vessel growth, and explore how biochemical and mechanical signals work together to regulate this process.	Frontiers in Cardiovascular Medicine
8	Ryu et all, 2021	Oscillatory shear stress promotes angiogenic effects in arteriovenous malformations endothelial cells.	The findings suggest a potential mechanism by which shear stress contributes to the development of AVMs, providing insights into the physiological processes involved.	The exact bodily processes that cause arteriovenous malformations (AVMs) are still unclear, making it hard to understand how and when they form. This uncertainty also makes it difficult to find effective treatments and predict how patients will respond.	Studying how shear stress leads to abnormal blood vessel growth in AVMs could help us better understand what causes them. This may support the development of genetic tests and more effective treatments.	Molecular Medicine (BioMed Central)

9	Moure et all, 2022	A coupled stochastic differential reaction-diffusion system for angiogenesis	The paper provides insights into the complex interactions between interstitial flow and chemokine matrix-binding affinity, which are crucial for understanding angiogenesis.	It is difficult to design experiments that truly reflect conditions controlled by both blood flow and chemokines. This is because the vascular network, interstitial flow, and different chemokine forms are closely linked, making setup and result interpretation more complex.	Future research could look at how fluid between tissues helps new blood vessels grow. It should also study how different flow levels and chemokine types affect this process, including how attached and free chemokines compete in different areas.	Dental science reports
10	Chen et all, 2023	Antiangiogenic therapy for ocular diseases: Current status and challenges	Overall, the research offers useful insights into existing treatments and future approaches, which could help improve care for ocular neovascular diseases.	Limited efficacy and unresponsiveness in many patients are significant challenges associated with anti-VEGF treatments for ocular neovascular diseases, indicating that not all patients benefit from the current therapies.	Research is needed to solve problems with current anti-VEGF treatments, like low effectiveness, lack of response in some patients, and drug resistance, to better help people with eye diseases involving abnormal blood vessel growth.	Journal of future medicine
11	Zhang et all, 2024	Mechanisms of angiogenesis in tumour	It shows how tumors can use other types of blood vessel growth, not just sprouting, to avoid antiangiogenic treatments, helping us better understand why some tumors resist therapy.	Overcoming resistance to antiangiogenic therapy is a major challenge in cancer treatment. Tumors can avoid these therapies by using other ways to grow blood vessels, bringing in helpful bone marrow cells, or adjusting to low oxygen levels to keep growing.	Future research could look at how bone marrow-derived cells (BMDCs) help tumors grow blood vessels and avoid the immune system. Learning how different BMDCs work could lead to new treatment options and make current therapies more effective.	Frontiers in Oncology
12	Yao et all, 2023	Angiogenesis in hepatocellular carcinoma: mechanisms and anti-angiogenic therapies	It shows how different pro-angiogenic factors and the tumor environment help blood vessels grow, giving clues for new targets in anti-angiogenic treatments.	Current anti-angiogenic treatments for liver cancer (HCC) offer only small survival benefits, showing the need to find new targets and better strategies to make these treatments more effective.	More studies are needed to learn how blood vessels grow in different forms of liver cancer (HCC). This could help find new treatment targets and improve patient outcomes.	Cancer biology and medicine

Study Characteristics

Following a systematic literature selection process using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) framework, a total of 12 relevant peer-reviewed articles were identified and included in this review. These articles were selected based on their specific focus on the influence of hydrodynamic forces such as shear stress, matrix compression, and interstitial flow on angiogenesis, with particular attention to endothelial cell behavior and vascular remodeling across physiological and pathological contexts.

The selected studies exhibit a diverse array of experimental methodologies and application areas. For instance, Campinho et al. (2020) and Gordon et al. (2020) employed advanced in vitro models, including microfluidic systems and synthetic hydrogels, to examine how shear stress and cyclic strain influence endothelial cell migration, polarization, and vascular sprouting. These platforms provide controllable environments for mechanobiological investigations, although they still face limitations in mimicking the full complexity of in vivo vascular systems.
In contrast, Ruehle et al. (2020) addressed the impact of extracellular matrix (ECM) compression on microvascular angiogenesis, emphasizing the temporal sensitivity of mechanical loading during tissue regeneration. Complementing these empirical approaches, Moure et al. (2022) developed a computational model simulating the coupled effects of interstitial fluid flow and chemokine gradients, offering insights into the spatial and chemical regulation of angiogenesis under biomechanical conditions.

Several studies explored mechanical forces in disease contexts. Ryu et al. (2021) investigated how oscillatory shear stress promotes pathological angiogenesis in arteriovenous malformations (AVMs) using endothelial cells from patient samples, while Russo et al. (2020) analyzed how altered shear stress contributes to endothelial dysfunction and extracellular matrix remodeling, processes involved in diseases such as atherosclerosis and thrombosis. Similarly, Miller et al. (2022) and Flouroy et al. (2022) provided molecular perspectives by examining mechanosensitive signaling pathways like VEGFR-2 and integrins, elucidating how mechanical forces interact with angiogenic pathways at the cellular level.

Further, studies by Zhang et al. (2024) and Yao et al. (2023) extended this knowledge to tumor angiogenesis, showing how hypoxia and mechanical adaptation facilitate resistance to antiangiogenic therapies in cancer. Chen et al. (2023) addressed similar therapeutic challenges in ocular neovascular diseases, emphasizing the limited efficacy of current anti-VEGF strategies and the possible influence of biomechanical conditions on treatment resistance.

Lastly, Naito et al. (2022) offered a broader conceptual analysis of endothelial cell heterogeneity, suggesting that not all endothelial populations respond similarly to mechanical stimuli, which may explain variability in angiogenic responses across tissue types and disease states.

In summary, these 12 studies provide a rich and multidisciplinary foundation for understanding the biomechanical regulation of angiogenesis, spanning fundamental mechanisms, disease models, and therapeutic implications.

Emerging Themes

Through analysis of the 12 selected articles, several key themes have emerged that collectively advance our understanding of how hydrodynamic forces regulate angiogenesis. These themes span from the mechanosensitive behavior of endothelial cells to the complex integration of mechanical and biochemical signals in both physiological and pathological contexts.

Shear Stress as a Primary Biomechanical Regulator

A dominant theme across the literature is the critical role of shear stress in directing endothelial cell (EC) behavior and blood vessel morphogenesis. Laminar shear stress, typically associated with physiological blood flow, promotes endothelial alignment, stability, and quiescence, while oscillatory or disturbed shear stress triggers endothelial activation, inflammation, and angiogenesis. Campinho et al. (2020) and Russo et al. (2020) illustrate that altered shear stress modulates endothelial adhesion, cytoskeletal rearrangement, and extracellular matrix remodeling—processes essential for both vascular sprouting and pathological remodeling.

Ryu et al. (2021) extend this concept by demonstrating that oscillatory shear stress contributes to the angiogenic phenotype of endothelial cells in arteriovenous malformations (AVMs), suggesting that abnormal flow patterns can initiate disease-specific vascular changes.

Mechanotransduction and Signal Integration

Another emerging theme is the molecular transduction of mechanical stimuli into intracellular signaling pathways, also known as mechanotransduction. Studies such as those by Flouroy et al. (2022) and Miller et al. (2022) emphasize how mechanical forces activate key angiogenic receptors and signaling networks, including VEGFR-2, integrins, MAPK, and Notch. These pathways mediate the cellular response to flow and stretch by altering gene expression, proliferation, and migration.

Interestingly, the reviewed literature indicates that mechanical signals do not function in isolation. Rather, they interact dynamically with biochemical cues. For example, Miller et al. describe how VEGFR-2 activity is modulated not only by VEGF ligands but also by the surrounding mechanical environment, highlighting the synergistic relationship between physical and chemical signals in angiogenesis.

Flow Directed Spatial Patterning of Angiogenesis

Flow is not only a stimulus but also a spatial organizer of angiogenesis. Studies by Gordon et al. (2020) and Ruehle et al. (2020) suggest that blood flow and matrix tension can influence where and when blood vessels sprout, through directional migration, cell elongation, and flow-induced polarization of endothelial cells. The timing and orientation of flow also determine the distribution of angiogenic factors, such as VEGF and chemokines, which guide vessel branching.

Endothelial Cell Heterogeneity and Flow Responsiveness

Emerging evidence from Naito et al. (2022) and others points to significant heterogeneity among endothelial cells, particularly in their proliferative capacity and mechanosensitivity. Some subpopulations may be more responsive to shear stress or matrix deformation, which has implications for both regenerative medicine and targeted therapy. Understanding which ECs are flow-responsive is key to developing cell-specific interventions.

Clinical and Regenerative Applications of Mechanical Angiogenesis

Lastly, a growing theme across studies is the therapeutic potential of biomechanical modulation. Ruehle et al. (2020) and Gordon et al. (2020) suggest that mechanical loading strategies—such as matrix compression or engineered flow fields—can be harnessed to enhance vascularization in tissue grafts and wound healing. Meanwhile, computational insights from Moure et al. (2022) may inform the rational design of flow-based regenerative systems in bioengineering and surgical applications.

Research Gaps and Challenges

Despite substantial progress in understanding the biomechanical regulation of angiogenesis, several significant research gaps and challenges remain across the reviewed literature. A primary limitation lies in the inadequacy of current in vitro models to accurately replicate physiological blood flow conditions. While systems such as microfluidic devices and synthetic hydrogels offer control over certain parameters, they often fail to incorporate critical in vivo elements such as tissue-level stiffness gradients, pulsatile flow dynamics, and the presence of support cells. This limits the generalizability of mechanobiological findings to clinical or whole-organism contexts. Additionally, there is a lack of standardization in the application and measurement of mechanical forces, with studies employing widely varying magnitudes, flow profiles, and exposure times, making cross-comparison difficult. Another major challenge is the incomplete understanding of mechanotransduction pathways. Although receptors like VEGFR-2 and integrins have been identified as flow-sensitive regulators, the downstream molecular signaling mechanisms by which mechanical stimuli influence gene expression and endothelial behaviour remain poorly defined, particularly when these signals interact with concurrent biochemical cues.

Moreover, emerging research has pointed to the heterogeneity of endothelial cells as a potential factor in varied mechanosensitivity, yet few studies have examined how specific endothelial subpopulations respond differently to hydrodynamic forces. This knowledge gap limits the development of targeted mechanotherapeutic strategies. Similarly, while most studies focus on shear stress within blood vessels, relatively little attention has been paid to interstitial flow, which plays a key role in regulating tissue-level chemokine gradients and extracellular matrix remodeling. The computational models that do explore this area, such as those presented by Moure et al., still require extensive experimental validation. Importantly, the translation of biomechanical insights into clinical therapies remains underdeveloped. For instance, antiangiogenic treatments for cancer and ocular diseases often show limited efficacy, in part because they fail to consider how mechanical adaptations in neovascular tissue contribute to therapeutic resistance. Finally, the use of human-derived endothelial cells crucial for disease-specific research faces ethical and technical barriers, including limited availability and donor variability. Altogether, these challenges underscore the need for more integrative, standardized, and translational approaches to fully harness the potential of biomechanical regulation in angiogenesis.

CONCLUSION AND SUGGESTION

This review has highlighted the growing body of evidence demonstrating that hydrodynamic forces including shear stress, interstitial flow, cyclic strain, and matrix compression play a central role in regulating angiogenesis. These mechanical stimuli influence critical aspects of endothelial cell behavior, such as proliferation, migration, alignment, and permeability, while also activating mechanosensitive pathways like VEGFR-2, integrins, and Notch signaling. Through the analysis of twelve selected studies, it becomes clear that biomechanical cues not only affect vascular patterning and morphogenesis under normal physiological conditions but also contribute to pathological angiogenesis in diseases such as cancer, ocular disorders, and arteriovenous malformations.

Despite significant advances, several challenges persist. Current in vitro models often fail to fully replicate the complexity of in vivo vascular environments, and there is a lack of standardization in how mechanical forces are applied and measured across studies. Moreover, the precise mechanisms

of mechanotransduction remain only partially understood, and the heterogeneity of endothelial cell responses to flow is still underexplored. Importantly, the clinical translation of mechanobiological knowledge into targeted therapies remains in its early stages.

Future research should focus on developing more physiologically relevant models, employing single cell profiling techniques, and integrating computational simulations with experimental systems. Doing so will enhance our ability to manipulate vascular growth through mechanical strategies and unlock new avenues in regenerative medicine, anti-angiogenic therapy, and vascular disease management.

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