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EXPLORING THE ROLE OF ANGIOGENESIS IN CANCER PROGRESSION AND THERAPY: UNLOCKING POTENTIAL TARGETS FOR PRECISION TREATMENT STRATEGIES –A SHORT REVIEW

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Abstract

Angiogenesis is a crucial process in cancer progression, supporting tumor growth, metastasis, and resistance to therapy. Targeted therapies have been developed to disrupt this process, improving treatment outcomes for cancer patients. Dysregulated angiogenesis ensures the supply of nutrients and oxygen to tumours, promoting their proliferation and spread to distant sites. Therapeutic interventions targeting angiogenesis, such as VEGF and angiopoietin inhibitors, have shown effectiveness in inhibiting tumor angiogenesis and enhancing patient survival across various cancer types. However, resistance to these therapies remains a significant challenge, necessitating the exploration of alternative and combination approaches to overcome resistance mechanisms. Advancements in molecular profiling and precision medicine have identified novel targets involved in angiogenesis, enabling the development of personalized treatment strategies. Biomarkers predictive of response to anti-angiogenic therapy aid in patient stratification and treatment selection. Additionally, innovative modalities like combination therapies and immunotherapy are being investigated to enhance treatment efficacy and combat resistance. Understanding the role of angiogenesis in cancer progression and therapy is essential for devising effective precision treatment strategies. Continued research efforts aimed at unraveling the complexities of angiogenesis and identifying novel therapeutic targets hold promise for improving treatment outcomes and advancing personalized cancer care.

Keywords: Angiogenesis, Cancer Treatment, Metastasis, Anti-Angiogenic Agents, Angiopoietin Inhibitors.

INTRODUCTION

Cancer angiogenesis, the process by which new blood vessels form to supply tumours with oxygen and nutrients, is a fundamental aspect of tumour growth and progression(Rajabi and Mousa 2017). Angiogenesis is tightly regulated in healthy tissues but becomes dysregulated in cancer, leading to the formation of abnormal blood vessels that support the rapid proliferation of malignant cells. This intricate process involves a complex interplay of signalling molecules, cellular interactions, and environmental factors(Janmey 1998). Tumour cells release angiogenic factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF), which stimulate nearby endothelial cells to sprout and form new blood vessels. Additionally, the tumour microenvironment, characterized by hypoxia and inflammation, further promotes angiogenesis by enhancing the expression of angiogenic factors and recruiting endothelial progenitor cells. As the tumour vasculature develops, it becomes irregular and leaky, facilitating the dissemination of cancer cells into the bloodstream and promoting metastasis(Magalhães and Dias 2019). Moreover, angiogenesis plays a crucial role in supporting tumour growth by providing a constant supply of nutrients and oxygen,

allowing cancer cells to thrive even in hostile conditions. Targeting angiogenesis has emerged as a promising therapeutic strategy in cancer treatment, with several anti-angiogenic agents approved for use in various malignancies. These agents inhibit angiogenesis by targeting key molecules involved in the process, such as VEGF and its receptors, disrupting tumour blood supply and impeding tumour growth. Despite advancements in anti-angiogenic therapy, challenges such as drug resistance and adverse effects remain, underscoring the need for further research to improve treatment outcomes(Zhang, Mozaffari et al. 2023). Additionally, combination approaches incorporating anti-angiogenic agents with other modalities such as chemotherapy, immunotherapy, and radiation therapy hold promise for enhancing efficacy and overcoming resistance mechanisms. Furthermore, understanding the molecular mechanisms underlying cancer angiogenesis is essential for the development of novel therapeutic targets and personalized treatment strategies. Advances in technologies such as genomics, proteomics, and imaging have provided insights into the intricate regulation of angiogenesis and identified potential biomarkers for patient stratification and monitoring treatment response(Chand, Keller et al. 2018). Additionally, preclinical models and innovative experimental approaches have facilitated the discovery of novel anti-angiogenic agents and therapeutic combinations, paving the way for translational research and clinical trials. In conclusion, cancer angiogenesis is a multifaceted process that plays a pivotal role in tumour growth and progression(Chakraborty, Jain et al. 2006). Targeting angiogenesis represents a promising avenue for cancer therapy, with ongoing efforts focused on improving treatment efficacy and patient outcomes through innovative approaches and personalized medicine.

Angiogenic induction in Cancer – A critical Challenge for therapy

Angiogenic induction in cancer represents a critical step in tumour progression, wherein tumours stimulate the formation of new blood vessels to support their growth and dissemination(Jiang, Wang et al. 2020). One of the most prominent examples of angiogenic induction in cancer is the upregulation of vascular endothelial growth factor (VEGF) signalling. Various cancers, including colorectal, breast, lung, and renal cell carcinoma, exploit VEGF to promote angiogenesis. Elevated levels of VEGF are associated with increased micro vessel density, tumour aggressiveness, and poor prognosis. Additionally, hypoxia-inducible factor 1-alpha (HIF-1α), a key regulator of cellular response to hypoxia, plays a pivotal role in angiogenic induction by upregulating VEGF expression in tumour cells under low oxygen conditions(Shi and Fang 2004). HIF-1α activation is observed in a wide range of cancers, including glioblastoma, pancreatic cancer, and ovarian cancer, driving angiogenesis and tumour progression. Furthermore, angiopoietin-2 (Ang-2) has emerged as a critical mediator of angiogenic induction in cancer. Ang-2 destabilizes blood vessels and promotes endothelial cell sprouting, facilitating the formation of new vessels in the tumour microenvironment(Zimna and Kurpisz 2015). High levels of Ang-2 are associated with increased tumour vascularity, metastasis, and poor clinical outcomes in several malignancies, including melanoma, prostate cancer, and hepatocellular carcinoma. Biomarkers play a crucial role in identifying tumours with heightened angiogenic potential and predicting response to anti-angiogenic therapies(D'Aniello, Berretta et al. 2019). For instance, in breast cancer, overexpression of VEGF and high micro vessel density assessed by immunohistochemistry are associated with increased angiogenic activity and resistance to chemotherapy. Similarly, in glioblastoma,

elevated levels of HIF-1α and VEGF in tumour tissues correlate with tumour aggressiveness and poor patient survival. Circulating biomarkers such as circulating endothelial cells (CECs) and angiogenic factors (e.g., VEGF, Ang-2) provide non-invasive indicators of angiogenic activity and treatment response(Senhaji, Squalli Houssaini et al. 2022). In colorectal cancer, elevated levels of circulating VEGF and Ang-2 have been associated with advanced disease stage, metastasis, and poor prognosis(Goede, Coutelle et al. 2010). Molecular imaging techniques, such as positron emission tomography (PET) and magnetic resonance imaging (MRI), enable the visualization and quantification of angiogenic biomarkers in vivo. For example, PET imaging with radiolabelled VEGF ligands allows for the assessment of VEGF expression levels in tumours, aiding in treatment selection and monitoring response to anti-angiogenic therapy(Michalski and Chen 2011). Similarly, MRI with contrast agents targeting angiogenic biomarkers provides valuable information on tumour vascularity and response to treatment in various cancers, including lung cancer and glioblastoma. In conclusion, angiogenic induction in cancer involves complex interactions between tumour cells, stromal cells, and the microenvironment, driving the formation of new blood vessels to support tumour growth and metastasis. Biomarkers play a crucial role in identifying tumours with heightened angiogenic potential and guiding personalized treatment strategies, thereby improving outcomes for cancer patients(Sveen, Kopetz et al. 2020).

Challenges of apoptosis in cancer angiogenesis

Apoptosis, a programmed cell death mechanism crucial for maintaining tissue homeostasis, is intricately involved in cancer angiogenesis, presenting unique challenges in the context of tumour progression(De Palma, Biziato et al. 2017). Dysregulation of apoptosis pathways can promote abnormal angiogenesis, facilitating tumour growth and metastasis (Whiteside 2008). For instance, overexpression of anti-apoptotic proteins such as Bcl-2 and Bcl-xL can confer resistance to apoptosis in cancer cells, promoting angiogenesis and tumour survival. Additionally, activation of pro-survival signalling pathways such as the PI3K/Akt pathway can suppress apoptosis and stimulate angiogenesis in cancer(Ciuffreda, McCubrey et al. 2009). Conversely, dysregulation of pro-apoptotic proteins, such as p53 and Bax, can compromise apoptosis and promote tumour angiogenesis. Furthermore, interactions between cancer cells and the tumor microenvironment play a critical role in modulating apoptosis and angiogenesis. Tumor-associated stromal cells, including cancer-associated fibroblasts and immune cells, can secrete pro-angiogenic factors and inhibit apoptosis in cancer cells, fostering tumor angiogenesis and progression(Liu, Zhou et al. 2019). Notably, the crosstalk between apoptosis and angiogenesis pathways is bidirectional, with angiogenic factors such as VEGF and FGF also influencing apoptosis in cancer cells. Overcoming the challenges of apoptosis dysregulation in cancer angiogenesis requires targeted therapeutic strategies(Cook and Figg 2010). For example, small molecule inhibitors targeting anti-apoptotic proteins such as Bcl-2 have shown promising results in preclinical studies and clinical trials, sensitizing cancer cells to apoptosis and suppressing tumor angiogenesis. Similarly, inhibitors of pro-survival signalling pathways such as PI3K/Akt have demonstrated efficacy in inhibiting angiogenesis and overcoming apoptosis resistance in cancer. Moreover, combination therapies targeting both angiogenesis and apoptosis pathways hold potential for synergistic effects and improved treatment outcomes in cancer patients(Berndsen, Abdul et al. 2017). Overall, understanding the

complex interplay between apoptosis and angiogenesis in cancer is essential for developing effective therapeutic approaches to combat tumor progression and metastasis.

Regulation of cancer angiogenesis

The regulation of cancer angiogenesis is a complex process involving a multitude of interconnected signaling pathways that dictate the formation of new blood vessels to sustain tumor growth(Bielenberg and Zetter 2015). One key pathway in this regulation is the vascular endothelial growth factor (VEGF) pathway. VEGF, produced by tumor cells and stromal cells in the tumor microenvironment, binds to its receptors (VEGFRs) on endothelial cells, stimulating their proliferation, migration, and survival, thereby promoting angiogenesis(Yang, Yan et al. 2018). Dysregulation of the VEGF pathway is frequently observed in various cancers, leading to excessive and aberrant blood vessel formation. Another critical pathway involved in cancer angiogenesis is the fibroblast growth factor (FGF) pathway. FGFs, produced by tumor cells and surrounding stromal cells, bind to FGF receptors (FGFRs) on endothelial cells, activating downstream signalling cascades that promote angiogenesis(Korc and Friesel 2009). Additionally, angiopoietin-Tie signalling plays a crucial role in regulating angiogenesis. Angiopoietins, particularly Ang-1 and Ang-2, interact with their receptor Tie-2 on endothelial cells to modulate vessel stability and permeability, influencing the sprouting and remodelling of blood vessels within the tumor microenvironment. Furthermore, the Notch signalling pathway contributes to angiogenesis regulation by controlling endothelial cell fate and vessel branching. Notch ligands expressed on endothelial cells interact with Notch receptors on neighbouring cells, triggering signalling events that influence endothelial cell proliferation, migration, and vessel maturation. Moreover, the phosphoinositide 3-kinase (PI3K)/Akt/mTOR pathway plays a critical role in angiogenesis regulation by integrating signals from growth factors, cytokines, and oncogenic mutations to promote endothelial cell survival and proliferation. Dysregulation of the PI3K/Akt/mTOR pathway is frequently observed in cancer, leading to enhanced angiogenesis and tumor progression. Additionally, the transforming growth factor-beta (TGF-β) pathway exerts both pro-angiogenic and anti-angiogenic effects depending on context, highlighting its complex role in cancer angiogenesis regulation. TGF-β signalling influences endothelial cell behaviour, extracellular matrix remodelling, and immune cell function within the tumor microenvironment, ultimately impacting angiogenesis dynamics. Notably, these pathways interact with each other and with various other signalling networks in a highly interconnected manner to finely orchestrate the angiogenic response in cancer. Understanding the intricate regulation of cancer angiogenesis pathways is critical for developing targeted therapies aimed at disrupting tumor blood supply and inhibiting tumor growth and metastasis. Efforts to identify and target key molecular players within these pathways hold promise for improving treatment outcomes and overcoming resistance mechanisms in cancer patients.

Challenges in Cancer Angiogenic therapy

Cancer angiogenic therapy faces several challenges despite significant advancements in understanding the molecular mechanisms underlying tumor angiogenesis. One primary obstacle is the development of resistance to anti-angiogenic agents. While drugs targeting vascular endothelial growth factor (VEGF) signalling, such as bevacizumab, have shown efficacy in several cancers, resistance

can arise due to tumor heterogeneity, compensatory angiogenic pathways, and adaptive responses within the tumor microenvironment. For instance, preclinical studies have identified alternative angiogenic pathways, including fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) signalling, as potential mediators of resistance to VEGF inhibition. Clinical evidence also suggests that tumor cells can adapt to anti-angiogenic therapy by upregulating pro-angiogenic factors and recruiting alternative blood supply routes, leading to treatment failure and disease progression. Additionally, the normalization of tumor vasculature poses a challenge in cancer angiogenic therapy. While anti-angiogenic agents aim to prune abnormal and leaky blood vessels, promoting vessel normalization and improving drug delivery, this process can paradoxically enhance tumor invasiveness and metastasis. Recent studies have highlighted the role of pericyte coverage and vessel maturation in determining the effectiveness of anti-angiogenic therapy, emphasizing the need for strategies to modulate vascular normalization without promoting tumor aggressiveness. Moreover, the adverse effects associated with anti-angiogenic therapy present another challenge in cancer treatment. Common side effects include hypertension, proteinuria, bleeding, thrombosis, and impaired wound healing, which can compromise patient quality of life and necessitate dose adjustments or treatment interruptions. For example, clinical trials evaluating bevacizumab in colorectal cancer and non-small cell lung cancer have reported an increased risk of arterial thromboembolic events and gastrointestinal perforation, highlighting the importance of careful patient selection and monitoring(Benedito and Hellström 2013). Furthermore, resistance to anti-angiogenic therapy can be mediated by the tumor microenvironment, including interactions with cancer-associated fibroblasts, immune cells, and extracellular matrix components. Recent studies have uncovered the role of tumor-secreted factors, such as cytokines, chemokines, and extracellular vesicles, in modulating angiogenesis and promoting resistance to anti-angiogenic therapy(Benedito and Hellström 2013). For instance, cancer-associated fibroblasts can secrete pro-angiogenic factors and remodel the extracellular matrix, creating a supportive niche for tumor growth and metastasis(Benedito and Hellström 2013). Similarly, immune cells within the tumor microenvironment can release angiogenic cytokines and promote vascular remodeling, contributing to therapy resistance. Addressing these challenges in cancer angiogenic therapy requires innovative strategies and combination approaches to overcome resistance, minimize adverse effects, and improve patient outcomes. Emerging therapeutic strategies include targeting alternative angiogenic pathways, disrupting tumor-stromal interactions, and enhancing immune-mediated anti-tumor responses(Laplagne, Domagala et al. 2019). For example, combination therapies incorporating anti-angiogenic agents with immunotherapy, chemotherapy, or targeted therapy have shown promise in preclinical models and early clinical trials. Additionally, the development of predictive biomarkers and imaging techniques can help identify patients who are likely to benefit from angiogenic therapy and monitor treatment response in real time, facilitating personalized treatment strategies. Overall, while challenges persist in cancer angiogenic therapy, ongoing research efforts hold promise for addressing these obstacles and improving the efficacy of anti-angiogenic agents in the treatment of cancer(Kargozar, Baino et al. 2020).

Future perspectives in Cancer Angiogenesis

Future perspectives in cancer angiogenic therapy hold promise for revolutionizing cancer treatment by leveraging emerging technologies and innovative strategies to overcome existing challenges and improve patient outcomes. One key avenue for advancement is the development of combination therapies that target multiple aspects of the angiogenic process, including vessel formation, stabilization, and maturation, to enhance efficacy and mitigate resistance mechanisms(Lopes-Coelho, Martins et al. 2021). For example, recent preclinical studies have demonstrated synergistic effects of combining anti-angiogenic agents with immunotherapy or chemotherapy, leading to improved tumor regression and prolonged survival in animal models. Additionally, the advent of precision medicine approaches, such as the identification of patient-specific biomarkers and molecular profiling of tumors, enables the selection of targeted therapies tailored to individual patients, maximizing therapeutic benefit while minimizing adverse effects. Furthermore, the integration of novel drug delivery systems, such as nanoparticles and liposomes, offers the potential to enhance the delivery of anti-angiogenic agents to tumor sites, improving drug bioavailability and penetration into the tumor microenvironment(Xu and Li 2023). Recent advancements in imaging modalities, including dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and positron emission tomography (PET), allow for real-time monitoring of angiogenic activity and treatment response, enabling clinicians to adapt treatment strategies based on patient-specific dynamics. Moreover, the development of next-generation anti-angiogenic agents, such as small molecule inhibitors targeting novel angiogenesis-related pathways or gene therapies aimed at modulating angiogenic gene expression, holds promise for overcoming resistance and expanding the therapeutic armamentarium against cancer(Workman 2015). Additionally, strategies aimed at targeting the tumor vasculature through vascular normalization, rather than outright vessel inhibition, have shown promise in preclinical models by improving drug delivery and immune cell infiltration into tumors, leading to enhanced treatment efficacy and reduced metastasis. The integration of artificial intelligence and machine learning algorithms into drug discovery and development processes facilitates the rapid identification of novel therapeutic targets and prediction of treatment responses, accelerating the translation of basic research findings into clinical applications(Tan, Thomas et al. 2009). Furthermore, the advent of gene editing technologies, such as CRISPR/Cas9, offers the potential to precisely manipulate angiogenic pathways within tumor cells or the tumor microenvironment, paving the way for personalized therapeutic interventions tailored to the molecular characteristics of individual tumors. In conclusion, future perspectives in cancer angiogenic therapy are characterized by a multidisciplinary approach leveraging advances in precision medicine, drug delivery, imaging, and novel therapeutic modalities to overcome existing challenges and revolutionize cancer treatment paradigms. Collaborative efforts between researchers, clinicians, and industry partners are essential for translating these promising innovations into clinical practice and ultimately improving outcomes for cancer patients(Waldman and Terzic 2011).

CONCLUSION

In conclusion, the exploration of angiogenesis in cancer progression and therapy has unveiled critical insights into tumor biology, highlighting its multifaceted role in driving disease advancement and treatment resistance. The development of targeted

therapies directed against angiogenic pathways, such as VEGF and angiopoietin inhibitors, has revolutionized cancer treatment, offering improved outcomes for patients across various malignancies. However, the emergence of resistance mechanisms poses a significant hurdle, necessitating innovative strategies and combination approaches to circumvent therapeutic limitations. Moreover, advances in molecular profiling and precision medicine have facilitated the identification of novel angiogenic targets, paving the way for personalized treatment regimens tailored to individual patients. Biomarkers predictive of treatment response enable precise patient stratification, optimizing therapeutic outcomes. Additionally, the exploration of combination therapies, including immunotherapy and agents targeting multiple angiogenic pathways, holds promise for enhancing treatment efficacy and overcoming resistance. Overall, comprehending the intricate interplay between angiogenesis, cancer progression, and therapy is paramount for devising effective precision treatment strategies. Continued research endeavours aimed at unravelling the complexities of angiogenesis and identifying novel therapeutic targets are essential for further improving treatment outcomes and advancing personalized cancer care in the quest for better patient outcomes and prolonged survival.

Conflict of interest

The authors declare no conflict of interest.

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