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Bispecific Antibodies in Angiogenesis Suppression: Expanding the Therapeutic Horizon

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Introduction

Angiogenesis—the formation of new blood vessels from pre-existing vasculature—is a critical process for tumor progression, invasion, and metastasis. It is one of the hallmarks of cancer, driven by an intricate interplay of pro-angiogenic factors, including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), angiopoietins, and others. Targeting angiogenesis has emerged as a fundamental pillar of modern oncology, exemplified by the widespread use of anti-VEGF therapies such as bevacizumab, aflibercept, and various tyrosine kinase inhibitors (TKIs). However, despite initial success, these therapies face limitations due to tumor adaptation, compensatory pathways, intrinsic and acquired resistance, and limited clinical efficacy in certain tumor types. These challenges have prompted the exploration of novel therapeutic strategies that can simultaneously target multiple angiogenic drivers. One such promising innovation is the development of bispecific antibodies (bsAbs)—engineered molecules designed to bind two distinct antigens or epitopes simultaneously [1,2].

Description

Bispecific antibodies are recombinant proteins engineered to simultaneously recognize two distinct epitopes, which may belong to the same or different molecules. The rationale for developing bsAbs lies in their ability to provide combinatorial targeting within a single molecular scaffold. This design allows for dual blockade of angiogenic pathways or coupling of an anti-angiogenic function with another therapeutic mechanism, such as T-cell redirection or immune checkpoint inhibition. There are several structural formats of bispecific antibodies, ranging from full-length immunoglobulin G (IgG)-like molecules with dual specificity to smaller constructs such as tandem single-chain variable fragments (scFvs), diabodies, and dual-affinity retargeting molecules (DARTs). These diverse architectures offer flexibility in pharmacokinetics, stability, and tissue penetration [3].

Preclinical studies demonstrated that faricimab effectively reduced vessel leakage, normalized vascular morphology, and inhibited tumor growth in xenograft models. In ophthalmology, where pathologic angiogenesis plays a role in diseases like age-related macular degeneration, faricimab has already received FDA approval, demonstrating its dual-targeting efficacy and safety. Its application in oncology is under active investigation, with early-phase trials evaluating its role in combination with immune checkpoint inhibitors or chemotherapeutic regimens. Faricimab exemplifies how bispecific targeting of VEGF-A and Ang-2 can provide synergistic inhibition of tumor angiogenesis and potentially delay resistance onset. Delta-like ligand 4 (DLL4), a Notch pathway ligand, has emerged as a key regulator of tumor angiogenesis and vascular maturation. Unlike VEGF, which stimulates angiogenesis, DLL4-Notch signaling acts as a negative regulator, promoting vessel pruning and stabilization. Paradoxically, tumor-associated DLL4 expression creates an abnormal feedback loop that enhances neovascular complexity while supporting tumor survival. Inhibition of DLL4 alone has shown anti-tumor effects but is associated with severe vascular toxicity due to overproliferation of immature vessels [4].

The clinical development of bispecific antibodies in oncology is accelerating, with numerous candidates in preclinical and early clinical stages. While ophthalmic applications have already validated bsAbs targeting VEGF and Ang-2, oncology poses unique challenges in terms of tumor heterogeneity, immunogenicity, and pharmacokinetics. Clinical trials evaluating bsAbs must carefully assess safety, particularly in regard to vascular toxicity, off-target effects, and immune-related adverse events. Furthermore, appropriate patient selection based on angiogenic and immunologic biomarkers will be critical to maximizing efficacy [5].

Conclusion

Bispecific antibodies represent a transformative advancement in the suppression of tumor angiogenesis, offering a strategic solution to the limitations of traditional monospecific therapies. By simultaneously targeting multiple proangiogenic ligands, receptors, or immune checkpoints, bsAbs disrupt the redundancy of the angiogenic network, enhance vascular normalization, and potentiate immune responses. Their versatility, mechanistic precision, and potential for synergy with existing modalities position them as powerful tools in the evolving paradigm of cancer therapy. While challenges remain in clinical translation, including safety, manufacturing, and patient stratification, the momentum behind bsAb development is undeniable. As the understanding of tumor vascular biology deepens and engineering platforms advance, bispecific antibodies are poised to expand the therapeutic horizon in oncology—moving beyond VEGF inhibition to a future of integrated, personalized, and durable antiangiogenic interventions. With continued innovation and rigorous clinical evaluation, bispecific antibodies may not only suppress angiogenesis but redefine how we treat solid tumors in the era of precision medicine.

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Conflict of Interest

None.

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