MLVs: Dual Role in Brain Metastases Offers Therapeutic Targets

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> Brain metastases remain a significant challenge in oncology, characterized by poor prognoses and treatment resistance. Recent insights into meningeal lymphatic vessels (MLVs) reveal their dynamic, bidirectional involvement in the progression of these intracranial malignancies, presenting novel therapeutic avenues for improved patient outcomes.1

KEY TAKEAWAYS

- The Pivot: MLVs, once thought to be solely beneficial, transition to promoting tumor dissemination and immunosuppression as brain metastases progress.
- The Data: Under physiological conditions, MLVs drain tumor antigens to cervical lymph nodes, supporting T-cell activation. In advanced disease, VEGF-C-driven pathological MLV remodeling facilitates tumor spread.1
- The Action: Future therapeutic strategies may involve enhancing MLV drainage for immunotherapy or inhibiting tumor-driven lymphangiogenesis to limit metastatic spread.

Brain metastases represent the most prevalent intracranial malignancies, and despite advancements in treatment, patient prognoses remain poor. This is largely attributable to significant treatment resistance and a highly restrictive tumor microenvironment.1 The rediscovery of meningeal lymphatic vessels (MLVs) has provided new insights into the brain's interaction with the immune system. MLVs are responsible for cerebrospinal fluid drainage, waste clearance, and immune cell trafficking, and their dysfunction is linked to various neurological diseases.1

The Dynamic Role of Meningeal Lymphatic Vessels

In the context of brain metastases, MLVs play a dynamic, dual role that evolves with the tumor microenvironment. Under physiological conditions or in the early stages of tumor development, MLVs function as a 'friend' by promoting anti-tumor immunity. They achieve this by draining tumor antigens to cervical lymph nodes and supporting T-cell activation.1 This mechanism contributes to the body's natural defense against early metastatic spread.1

However, as the tumor progresses, this beneficial role can reverse. Excessive tumor-derived factors, such as VEGF-C, induce pathological MLV remodeling. This structural change represents a critical switch, transforming MLVs into a 'foe'. Pathologically dilated MLVs then facilitate tumor dissemination, and their drainage dysfunction creates a local immunosuppressive niche, leading to immune evasion.1 This shift from immune support to metastatic promotion and immunosuppression highlights the complex interplay between MLVs and the evolving tumor microenvironment.1

The initial characterization of MLVs as a 'friend' involves their role in immune surveillance. By transporting antigens

from the brain parenchyma and subarachnoid space to regional lymph nodes, MLVs initiate adaptive immune responses. This process is crucial for the recognition and elimination of nascent tumor cells, thereby limiting the establishment and growth of micrometastases. The integrity and proper function of MLV drainage pathways are therefore essential for maintaining immune homeostasis within the central nervous system and preventing early metastatic seeding.1

Conversely, the transformation of MLVs into a 'foe' is driven by specific molecular signals emanating from the growing tumor. Vascular Endothelial Growth Factor C (VEGF-C), a well-established lymphangiogenic factor, is often overexpressed by various primary tumors that commonly metastasize to the brain, including lung cancer, breast cancer, and melanoma. This overexpression leads to aberrant MLV proliferation and dilation, creating conduits that can directly facilitate the egress of tumor cells from the brain into the systemic circulation, or to other intracranial sites. Furthermore, the dysfunctional drainage associated with pathologically remodeled MLVs contributes to the accumulation of immunosuppressive factors and immune cells, such as regulatory T cells and myeloid-derived suppressor cells, within the peritumoral microenvironment. This local immunosuppression further hinders effective anti-tumor immunity, allowing brain metastases to evade immune surveillance and progress unchecked.1

Implications for Future Therapeutic Strategies

The 'friend and foe' character of MLVs positions them as a potential therapeutic target. Strategies aimed at enhancing MLV drainage may improve the efficacy of immunotherapy and drug delivery to the brain. Conversely, inhibiting tumor-driven lymphangiogenesis could help limit metastatic spread.1 This review summarizes current knowledge on MLV biology, their interactions with brain metastases, and discusses potential strategies and challenges for targeting MLVs in future therapies.1

The current understanding of MLV biology and its interaction with brain metastases is primarily based on preclinical models and observational studies. The review did not present data from human clinical trials or specific therapeutic interventions. Therefore, while the conceptual framework is compelling, direct clinical applicability remains to be established through further research.1

The epidemiological burden of brain metastases underscores the urgent need for novel therapeutic approaches. Brain metastases occur in 20-40% of all cancer patients, with lung cancer, breast cancer, and melanoma being the most common primary tumor types. The median survival for patients with brain metastases remains poor, often ranging from months to a little over a year, depending on the primary tumor, number of lesions, and performance status. Current treatments, including surgery, radiation therapy, and systemic therapies, often face challenges due to the blood-brain barrier and the unique immunosuppressive environment of the brain. Targeting MLVs offers a promising avenue to overcome some of these limitations by modulating immune responses and potentially improving drug penetration.1

Future research will need to focus on developing specific MLV-targeting agents and validating their efficacy and safety in relevant animal models before progressing to human trials. This includes identifying specific molecular targets on MLVs that can be modulated without causing systemic side effects. Furthermore, the precise timing of MLV-targeted interventions will be critical, given their dual role. Early intervention aimed at enhancing MLV function might prevent metastatic establishment, while later interventions might focus on inhibiting pathological lymphangiogenesis to limit tumor progression and dissemination. Understanding the specific patient populations and tumor types that would most benefit from MLV-targeted therapies is also essential for successful clinical translation.1

For comprehensive insights into oncology's evolving landscape, encompassing the challenges of brain metastases and therapeutic strategies, consult the Oxford Handbook of Oncology.

CLINICAL IMPLICATIONS

The identification of meningeal lymphatic vessels (MLVs) as having a bidirectional role in brain metastases presents an intriguing, albeit early, avenue for therapeutic development. Clinicians currently face significant limitations in treating brain metastases, particularly given the challenges of drug delivery across the blood-brain barrier and the highly immunosuppressive microenvironment. The concept that MLVs could be manipulated, either to enhance immune responses or to inhibit metastatic spread, offers a novel perspective beyond conventional chemotherapy, radiation, or targeted agents.

For the pharmaceutical industry, this research points towards the potential for developing agents that specifically target MLV function. This could include lymphangiogenesis inhibitors to prevent tumor dissemination or, conversely, agents that enhance MLV drainage to improve the efficacy of existing immunotherapies or novel drug delivery systems. However, the 'friend and foe' nature of MLVs necessitates a precise understanding of when and how to intervene, as an ill-timed intervention could inadvertently promote disease progression. This complexity will require significant investment in preclinical and early-phase clinical trials to delineate optimal timing and mechanisms of action.

Patients with brain metastases face a grim prognosis, and any strategy that could improve treatment response or prevent recurrence would be highly impactful. While this research is foundational and not immediately actionable for prescribing clinicians, it provides a glimpse into future treatment paradigms. It underscores the ongoing need for research into the unique biology of brain metastases, moving beyond systemic disease models to address the specific challenges of the central nervous system. The ASCO 2026 discussion on evolving strategies for EGFR-mutated NSCLC and HR+/HER2- mBC, while not directly addressed by this specific paper, highlights the broader trend towards understanding and targeting the tumor microenvironment, of which MLVs are a critical, newly appreciated component.

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