Blocking Lymphatic Vessel Growth to Enhance Cancer Therapy

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In his famous *The Art of War*, Sun Tzu, the Chinese legendary military strategist from around 2,500 years ago, pointed out that cutting off the enemy's retreat routes – a tactic known as "closing the gates to catch the thief" – is sometimes critical to securing victory. Today, this battlefield principle is being reimagined in the fight against cancer.

Cancer, the uncontrolled growth of abnormal cells, remains one of the leading causes of death worldwide, challenging scientists to improve the efficacy of anti-cancer drugs.

Recent research published in the April 15 issue of *Signal Transduction and Targeted Therapy* reveals a promising breakthrough in cancer therapy. This study, led by Dr. ZHANG Yinlong from the University of Chinese Academy of Sciences (UCAS) and Dr. NIE Guangjun from the National Center for Nanoscience and Technology (NCNST), both under the CAS, introduces a new strategy to enhance drug accumulation in tumors.

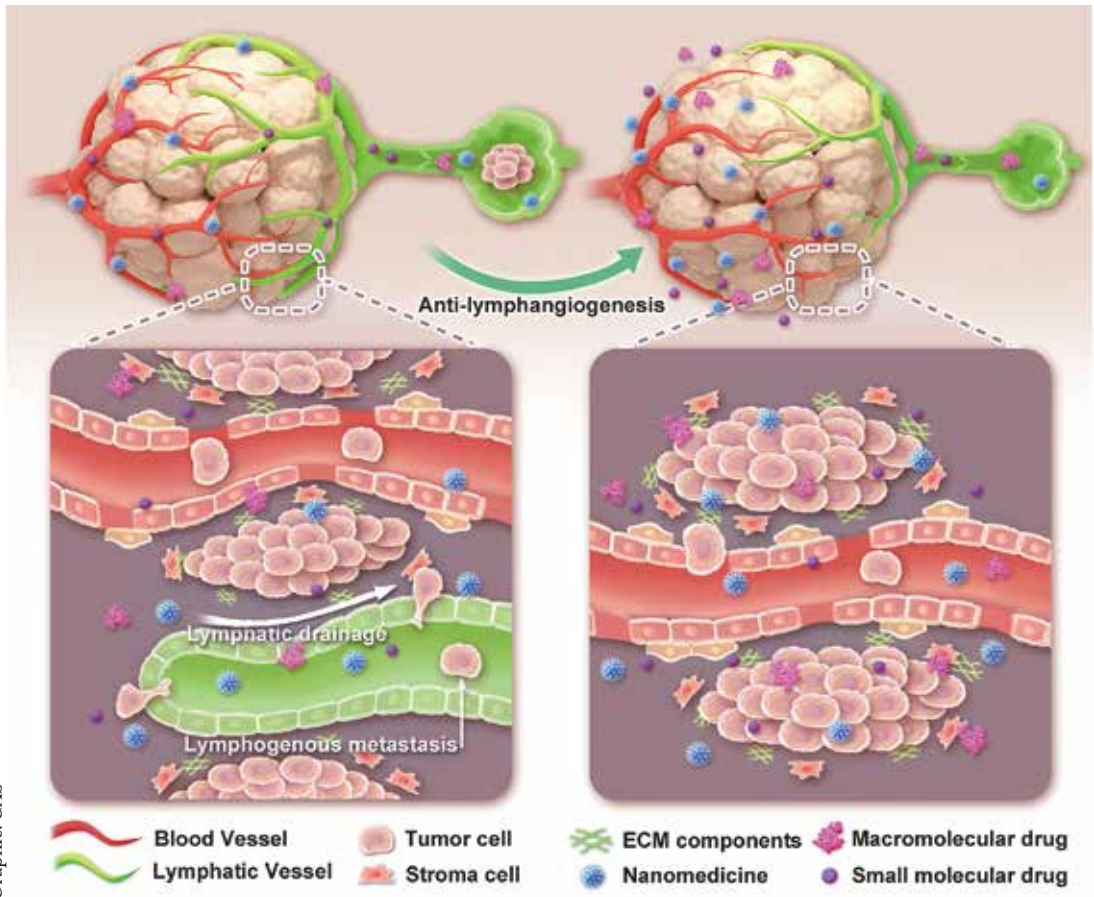
Cancer treatments often fail to precisely target the tumor, leading to inadequate drug accumulation at the cancer site and severe side effects. The inadequate drug accumulation is partly caused by the lymphatic system, primarily responsible for transporting lymph fluid, which contains nutrients, waste products, and immune cells throughout the body. In tumors, lymphatic vessels are crucial in draining fluid from the tumor microenvironment. This drainage is not merely a clearance mechanism but can also inadvertently facilitate the spread of cancer cells to other parts of the body and the removal of therapeutics from the tumor site. This quick removal reduces the dwell time of drugs within the tumor, diminishing their efficacy as less of the drug interacts with the cancer cells for a sufficient duration to exert its therapeutic effects.

The study's innovative approach centers on anti-lymphangiogenesis – blocking the growth of new lymphatic vessels within tumors, which can otherwise facilitate cancer spread and reduce treatment efficacy.

The researchers utilized two key substances: anlotinib, a multi-target tyrosine kinase inhibitor, and SAR131675, a selective inhibitor of the VEGFR-3 pathway, which is involved in lymphangiogenesis. These inhibitors showed significant success in reducing the density of lymphatic vessels in cancerous tissues in mouse models, thereby enhancing the concentration and efficacy of therapeutic drugs within tumors.

This method not only improves drug delivery but also mitigates one of the most daunting aspects of cancer treatment: metastasis – the spread of cancer cells to new areas. By curtailing the lymphatic routes that cancer cells can exploit to migrate, anti-lymphangiogenesis therapy significantly reduces the risk of metastasis, as demonstrated in the treated mice.

One of the most compelling aspects of this strategy is its dual



Graphic: CAS

A strategic siege on cancer by reducing the density of lymphatic vessels within the cancerous tissues simultaneously enhances cancer drug accumulation and cuts off the avenues for cancerous spread.

benefit. It hampers the cancer's ability to spread through lymphatic channels and boosts the immune response against tumors. The increased drug accumulation at the tumor site allows for more effective doses of chemotherapy and other treatments without increasing side effects, thereby enhancing overall treatment outcomes.

Furthermore, the study suggests combining this approach with existing therapies could lead to even better outcomes. For instance, when anlotinib was used alongside chemotherapy drugs like doxorubicin or immune checkpoint inhibitors like PD-L1 antibodies, there was a noticeable improvement in suppressing tumor growth and reducing metastasis compared to using these treatments alone.

"Our work describes a new, clinically transferrable approach to augmenting intratumoral drug accumulation, which shows great potential to address the current, unsatisfactory efficacies of therapeutic drugs without introducing metastatic risk," says the authors in the article.

By focusing on the lymphatic system within and around tumors, researchers are exploring a less conventional, potentially more fruitful pathway to enhance drug delivery and limit cancer progression. This approach leverages the body's own systems to combat the disease more effectively, providing a blueprint for future innovations in cancer treatment strategies.

Reference

Wang, C., Xu, J., Cheng, X., Sun, G., Li, F., Nie, G., & Zhang, Y. (2024). Anti-lymphangiogenesis for boosting drug accumulation in tumors. *Signal Transduction and Targeted Therapy*, 9(1), 89. doi:10.1038/s41392-024-01794-4