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RESEARCH HIGHLIGHT

Meningeal lymphatics "drain" brain tumors

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Lymphatic vessels in the brain meninges connect the brain to the periphery, and are implicated in controlling immune responses in the brain. Hu et al. demonstrate that the brain's rejection of glioma can be facilitated by expansion of the meningeal lymphatic vessels; similar findings were recently reported independently by Song et al.

Glioblastoma, a major subtype of glioma, is a malignant brain tumor. Afflicted patients cannot be saved by conventional treatments, which include surgical resection combined with radiation and chemotherapy. There is no therapy currently known to be effective against this lethal tumor. One promising strategy against glioblastoma involves the blockade of immune checkpoints. The most widely used experimental agents for blocking of an immune checkpoint are anti-PD-1 and anti-CTLA-4. These antibodies have indeed been found successful to differing extents in several mouse models of glioma.[1] Disappointingly, however, recent phase III clinical trials of glioblastoma resulted in failure.[2] Thus, an urgent need remains for the development of a novel therapeutic procedure that is effective against glioblastoma.

The failed initial attempts in clinical trials can be attributed to the unique immunological environment of the brain. No lymphatic vessels are housed in the brain parenchyma, but this does not mean that the brain is not surveyed by the immune system. Early research suggested an unconventional pathway, implicating lymphatics of the nasal mucosa as a communication route between the brain and cervical lymph nodes.[3] More recently, functional lymphatic vessels were found to be located in the meninges (in the dura mater), through which cerebrospinal fluid (CSF) drains into the deep cervical lymph nodes (dCLNs).[4] These dural meninges were also found to harbor a variety of immune cells.[5] In later work, the basal part of the skull meningeal lymphatic vessels was demonstrated to efficiently drain CSF.[6] Meningeal lymphatic vasculature has been shown to drain immune cells and to play a key role in neuroinflammation.[7] However, immunological aspects of these meningeal lymphatic vessels have only just begun to be appreciated, and their roles in diseases have mostly yet to be revealed.

In this issue of *Cell Research*, Hu and colleagues,[8] using a mouse model of brain tumor, reveal a crucial role for meningeal lymphatic vessels in the immune response to glioma. They show that overexpression by glioma cells of vascular endothelial growth factor (VEGF)-C, a growth factor for lymphatic endothelial cells (LECs), strengthens the anti-tumor effect of anti-PD-1/CTLA-4 antibodies. They show, moreover, that the effect of VEGF-C is mediated by the CCL21/CCR7 axis and mice treated with anti-CCL21 or CCR7 antibodies failed to benefit from VEGF-C. Hu and colleagues, after diligently analyzing the anatomy of meningeal lymphatics, found that tumor cell injection into the brain induced expansion of the dorsal meningeal lymphatics. Interestingly, the basal meningeal lymphatics showed only a marginal expansion, and nasal lymphatic vessels did not respond. To better address the role of the dorsal meningeal lymphatics, the authors photoablated the vessels with visudyne, as previously shown.[9] The result of this experiment, which left both nasal and basal lymphatics intact, showed that the reduction in tumor size and T-cell response evoked by anti-PD-1/CTLA-4 is dependent on dorsal meningeal lymphatics. Thus, these data emphasize the importance of the dorsal lymphatics in regulation of T-cell response to brain tumors.

A similar observation has been recently published by Song and colleagues.[10] Song and colleagues, using the adeno-associated virus to deliver VEGF-C to meningeal lymphatics in a mouse model, elegantly demonstrated that the virus induced rejection of glioma cells. Compared to untreated mice, VEGF-C-treated mice exhibited significantly more glioma-specific $CD8^+$ T cells in tumors and in dCLNs, and their rejection of glioma cells was indeed T-cell dependent. In glioblastoma tissues from patients treated with anti-PD-1, Song et al. found a positive correlation between mRNA levels of *Vegfc* and T-cell markers, indicating T-cell infiltration into the tumor site. Aiming at clinical application of their finding, Song et al. repeated their experiment using mRNA of VEGF-C, which offers a transient and less immunogenic method of delivery. Injection of VEGF-C mRNA into the mouse CSF, when accompanied by combined anti-PD-1/CTLA-4 treatment, had induced rejection of glioma. Accordingly, the authors proposed VEGF-C as a compelling novel therapeutic method against glioblastoma.

The precise role(s) of meningeal lymphatics in the context of tumor immunity remains elusive. As indicated by the work of Hu et al. it might simply be explained in terms of the VEGF-C-induced physical expansion of lymphatic vessels, thereby allowing enhanced CCL21/CCR7-dependent trafficking of immune cells. Another possible explanation is that VEGF-C might alter the biology of LECs. VEGF-C-treated meningeal LECs might foster the activation of antigen-presenting cells (APCs) in their vicinity, or might actively induce migration of antigen-loaded APCs to dCLNs, or might facilitate re-activation of antigen-specific T cells in situ. Transcriptome analysis of meningeal LECs and their surrounding immune cells exposed to VEGF-C should provide a clue to the exact role(s) played by meningeal lymphatics.

The two recent studies outlined above have not only proposed a novel therapeutic option worth trying against glioblastoma, but have also highlighted a crucial role of meningeal lymphatics in controlling a T-cell response to brain-derived antigens. Further investigation of meningeal lymphatics can be expected to reveal even more knowledge—and questions—about the fascinating properties of this lymphatic vasculature.

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ADDITIONAL INFORMATION

Competing interests: J.K. is a member of a scientific advisory group for PureTech Health and is holding patents and patent applications related to the findings described herein.

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