Expert Opinion on Therapeutic Targets

ISSN: 1472-8222 (Print) 1744-7631 (Online) Journal homepage: https://www.tandfonline.com/loi/iett20

Interstitial fluid flow under the microscope: is it a future drug target for high grade brain tumours such as glioblastoma?

Jennifer M. MunsonMunsonOEL

To cite this article: Jennifer M. MunsonMunsonOEL (2019) Interstitial fluid flow under the microscope: is it a future drug target for high grade brain tumours such as glioblastoma?, Expert Opinion on Therapeutic Targets, 23:9, 725-728, DOI: 10.1080/14728222.2019.1647167

To link to this article: https://doi.org/10.1080/14728222.2019.1647167

Accepted author version posted online: 25 Jul 2019.
Published online: 30 Jul 2019.

EXPERT OPINION ON THERAPEUTIC TARGETS
2019, VOL. 23, NO. 9, 725–728
https://doi.org/10.1080/14728222.2019.1647167

Taylor & Francis
Taylor & Francis Group

EDITORIAL

Interstitial fluid flow under the microscope: is it a future drug target for high grade brain tumours such as glioblastoma?

Jennifer M. Munson

Department of Biomedical Engineering & Mechanics, Virginia Polytechnic Institute & State University, Blacksburg, VA, USA

ARTICLE HISTORY Received 25 March 2019; Accepted 19 July 2019

1. What and where is interstitial fluid flow (IFF) in the brain?

IFF is the movement of fluid in the spaces between cells in tissue or interstitial space. In the brain, this space consists of a network of extracellular matrix co-mingled with a dense, process-rich network of astrocytes, microglia, and neurons. Fluid moves within the interstitial space as it drains toward open structures in and around the brain, and in 1998, Geer and Grossman observed that these bulk fluid flow pathways correlated with paths of tumor cell dissemination [1]. In fact, flow pathways such as the white matter tracts and ventricles are known impediments to treating glioblastoma.

2. Why is IFF important and how is it relevant in cancer?

Tumour progression is marked by an increase in fluid and solid stress due to influx of blood and other fluids into the tissue as well as accumulation of cells and extracellular matrix. The resulting heightened pressures (in patients undergoing standard of care treatment, ~3 mmHg) can be 2–10 times those of the adjacent healthy tissue, and this pressure gradient causes fluid flow from the tumor into the surrounding tissue [2] [3]. In vitro, applying IFF through engineered hydrogel systems stimulates brain tumor cell invasion both alone and towards gradients of growth factors[4,5]. In other cancers, this fluid flow is known to activate cells in the tissue around the tumor, further supporting disease progression [6].

3. What knowledge do we need to understand IFF in the context of brain cancers?

Currently, there are numerous gaps in our knowledge of fluid flow in the brain in general, let alone fluid flow in brain cancers. We are only just beginning to understand the nature of how fluid moves into, around, and out of the brain, and many previous findings remain highly debated. Additionally, the underlying physiological state of an organism has been shown to affect the rate, production, and movement of cerebrospinal fluid within the brain, including age, sex, disease state, circadian rhythm, etc. Though we know that there are changes to the bulk flows, definitive IFF rates, what flow means prognostically, the full repertoire of IFF's effects on tumor cells and other cells, and IFF's relationship to bulk flows, vascularization, and cerebral pressure are still murky.

4. Why can't we get there right now?

Currently, major impediments to the implementation of IFF as a target include a lack of understanding of 1) its nature in non-tumor conditions, 2) the variability of its magnitudes and patterns with tumors, 3) the diversity of responses to IFF on a cellular and tissue level, and 4) its complex effects on drug delivery and response. These can be remedied using methods (such as imaging) and inclusion in in vitro studies. Though we have made strides with these techniques, we have only scratched the surface of this ubiquitous force. However, tools for in vitro study (including hydrogel-based systems employing microfluidics) and in vivo imaging (including MRI and intravital imaging) have allowed us to begin assessing IFF, including the elucidation of several potential targets.

5. Known molecular targets (**Figure 1**)

IFF does not passively move tumor cells but in fact stimulates pathways overlapping with some known targets in GBM. There are two primary mechanisms identified as mediators of IFF-triggered invasion: 1) Autologous Chemotaxis is a mechanism whereby a cell stimulates its own migration via a self-secreted chemokine. When there is no convective force from fluid flow, the chemokine forms a diffuse, uniform cloud around the cell; however, if there is fluid flow, the chemokine is transported downstream of the cell forming a gradient along which the cell migrates. To mediate this mechanism, a cell must express both the chemokine and its receptor. For GBM the mediators of this mechanism have been identified as the ligand-receptor pair CXCL12 and CXCR4, both of which are overexpressed in many cancers and correlates with worsened survival. This flow-mediated invasion via CXCL12-CXCR4 has been shown both in vitro and in vivo [7]. Interestingly, this mechanism may be dependent on a number of microenvironmental factors including the rate of IFF and the density of tumor cells [8]. 2) Mechanotransduction occurs when a cell detects mechanical

CONTACT Jennifer M. Munson jm4kt@vt.edu @MunsonOEL Department of Biomedical Engineering & Mechanics, Virginia Polytechnic Institute & State University, BEAM (Mail code 0298), Kelly Hall 349, 325 Stanger Street, Blacksburg, VA 24061, USA

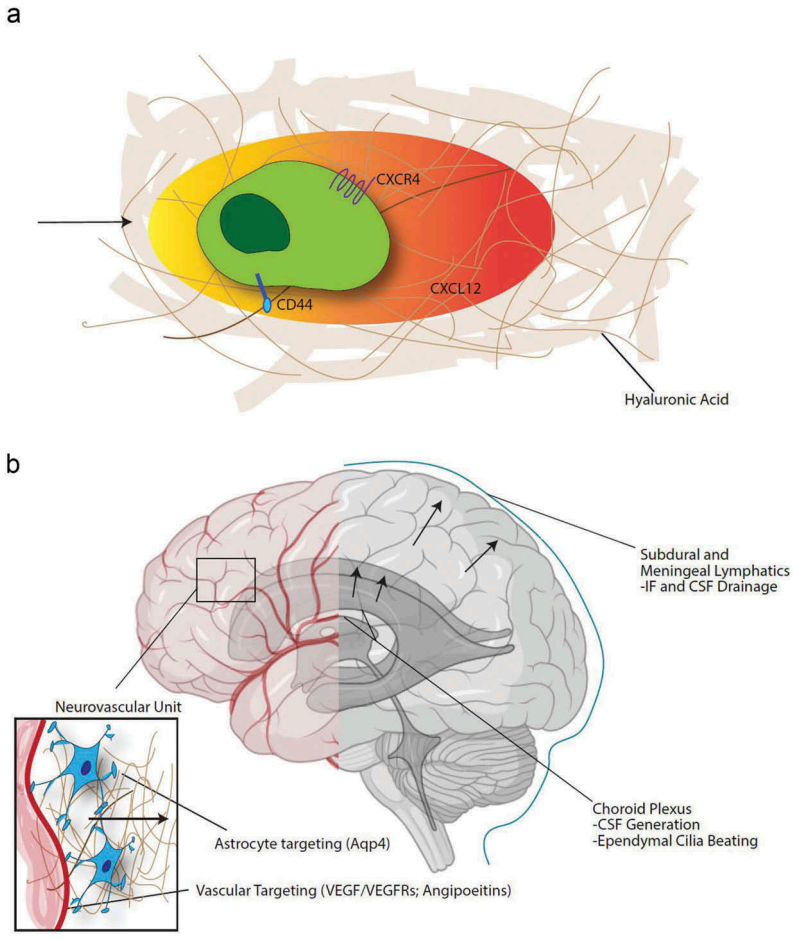

Figure 1. **Potential targets for interstitial fluid flow-mediated changes to glioblastoma** (a) Targets on glioma cells include the receptor CXCR4 (which can be targeted with AMD3100 (Plerixafor)) or its ligand CXCL12 as mediators of chemotactic invasion and CD44 and its substrate hyaluronic acid. (b) Fluid flow in the brain can be targeted via multiple exploratory targets including (clockwise from top right): Targeting of sites of drainage including subdural and meningeal lymphatics; targeting sites of CSF generation and movement in the choroid plexus lining the ventricles; targeting the neurovascular unit via blood vessels reducing leakage and the astrocytes increasing or altering fluid uptake via Aquaporins. (Brain image generated via Biorender).

changes to its surroundings, leading to signaling events and subsequent cell behaviors such as motility. Generally, IFF will deform the extracellular matrix and therefore the receptors bound to this matrix. In glioblastoma, the primary receptor currently implicated in this mechanism is the hyaluronan receptor, CD44, which is also correlated with worsened survival [5]. These two mechanisms of flow-stimulated invasion may act on distinct cell populations, suggesting dual-targeted therapies may be best for reducing glioblastoma invasion.

Other receptors and receptor-ligand pairs have been identified in other cancer to elicit flow-mediated invasion, such as CCR7-CCL21 and integrins [2]. There is an opportunity for more exhaustive testing and potential repurposing of therapies within the context of GBM. And although these are pathways that have been examined, there are other potential biomarkers and targets yet to be identified. Similarly, current research on tumor stiffness and detection of mechanical stress has identified targets that may overlap with IFF-stimulated invasion in the brain [9]. Fully integrating these varied approaches creates potential for multi-targeted therapeutics.

It is also possible to directly and therapeutically alter IFF itself by targeting major bulk flow mediators within and around the brain. These targets may be attractive because they are outside of the tumor and thus may have more predictable molecular targets across patients. Recent identification of new pathways of fluid movement and drainage from the brain offer unique opportunities to alter fluid flow. However, we do not yet understand the downstream effects of such changes and side effects (such as edema or seizure) could ensue when altering overall interstitial fluid pressures and fluid movement within this sensitive organ.

Sites of drainage, such as the meningeal and cribriform lymphatics, subarachnoid villi, and perivenous spaces, could offer a means to manipulate fluid flow at the outlet. This technique has been implemented in peripheral cancers (such as targeting or reducing lymphangiogenesis) but is a promising therapeutic strategy against GBM [10] [11]. Alternately, sites of influx, such as the blood vasculature and the choroid plexus, would allow alteration of incoming fluid to the brain and reduce overall fluid flow. Vascular targets such as VEGFR2 have been tried with glioblastoma

with less than promising survival effects [12]. Strategically altering flow throughout or within particular areas of the brain may impact GBM outcomes, but more research is necessary to understand the complex anatomical–physiological interactions. Sites of regulation within the brain include the glymphatic system [13], the ependymal cell layers [14], and glial cells. Targeting of any of these systems could result in vast changes to fluid flow though their impact on IFF is yet unknown. Targets on astrocytes within the glymphatic system, such as aquaporin-4, overlap with identified targets in GBM and thus IFF could play a role in this therapy [15].

6. Expert opinion: where are we headed with this research?

Intratumoral heterogeneity is a major impediment to understanding and treating individual tumors. These differences are both found within the tumor cells themselves, but also within the tissue surrounding the tumors. Recent mapping of IFF in tumors in vivo using MRI has shown high levels of differential flow and mass transport in and around implanted models of GBM [16]. These flows are different in both magnitude and direction and can vary quite dramatically in adjacent tissue regions. Interestingly, in mice, it appears that flow from the tumor may be governed more by the surrounding tissue structure than individual aspects of the tumor itself. This syncs well with data in patients suggesting that proximity to various structures (such as white matter tracts) are important prognostic factors. Related to the delivery of drugs, it may be advantageous to have more or less IFF depending on localization within the tumor. Based on the heterogeneity of the tissue flows that have been observed, it is likely that drug delivery and distribution is subject to these heterogeneous flow patterns and thus a major area for opportunity for strategic application of current therapies. Additionally, almost all of the current research has focused on the role of flow in invasion of tumor cells with little progress in the role of flow on other cellular behaviors such as cellular differentiation, genetic instability, metabolism, proliferation, and therapeutic response.

In total, IFF is an untapped well for potential drug research. Since we are not exploring how cells (any cells) respond in the presence of IFF we may be ignoring an entire set of genes, proteins, and other druggable targets that are only identifiable in the presence of flow. With the recent advent of imaging modalities, we can begin todetermine where in tumors IFF is heightened and use that information to discover new targets for therapy. I believe that this area of research coupled with better and simpler to implement preclinical in vitro screening models is the next step in using IFF as a biomarker and as a druggable target in GBM.

Acknowledgments

The author would like to thank Dr. R. Chase Cornelison for feedback.

Funding

This work supported by funding to JMM by National Cancer Institute [R37CA222563].

Declaration of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial relationships or otherwise to disclose.

ORCID

Jennifer M. Munson http://orcid.org/0000-0002-9477-1505

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Geer CP, Grossman SA. Interstitial fluid flow along white matter tracts: A potentially important mechanism for the dissemination of primary brain tumors. J Neurooncol. 1997;32(3):193–201.
2. Munson JM, Shieh AC. Interstitial fluid flow in cancer: implications for disease progression and treatment. Cancer Manag Res. 2014;6:317–328.
•• **In this review, interstitial fluid flow is described for a number of tumors and its effects on both tumor cells and the surrounding tumor microenvironment is exhaustively outlined giving a good primer on interstitial fluid flow in the context of all cancers, including glioblastoma.**
3. Boucher Y, Salehil H, Witwerl B, et al. Interstitial fluid pressure in intracranial tumours in patients and in rodents. Br J Cancer. 1997;75(6):829–836.
4. Munson JM, Bellamkonda RV, Swartz MA. Interstitial flow in a 3D microenvironment increases glioma invasion by a CXCR4-dependent mechanism. Cancer Res. 2013;73(5):1536–1546.
5. Qazi H, Shi ZD, Tarbell JM. Fluid shear stress regulates the invasive potential of glioma cells via modulation of migratory activity and matrix metalloproteinase expression. PLoS One. 2011;6(5):e20348.
6. Rutkowski JM, Swartz MA. A driving force for change: interstitial flow as a morphoregulator. Trends Cell Biol. 2007;17(1):44–50.
7. Cornelison RC, Brennan CE, Kingsmore KM, et al. Convective forces increase CXCR4-dependent glioblastoma cell invasion in GL261 murine model. Sci Rep. 2018;8(1):1–11.
• **This publication presents the first in vivo evidence that increasing interstitial fluid flow using convection enhanced delivery therapeutic techniques in mice will lead to a more invasive tumor. Subsequently, this invasion can be blocked by using AMD3100 (Plerixaflor) to inhibit CXCR4.**
8. Polacheck WJ, Charest JL, Kamm RD. Interstitial flow influences direction of tumor cell migration through competing mechanisms. Proc Natl Acad Sci. 2011;108(27):11115–11120.
9. Miroshnikova YA, Mouw JK, Barnes JM, et al. Tissue mechanics promote IDH1-dependent HIF1α-tenascin C feedback to regulate glioblastoma aggression. Nat Cell Biol. 2016;18(12):1336–1345.
10. Da Mesquita S, Louveau A, Vaccari A, et al. Functional aspects of meningeal lymphatics in ageing and Alzheimer's disease. Nature. 2018;560(7717):185–191.
11. Hsu M, Rayasam A, Kijak JA, et al. Neuroinflammation-induced lymphangiogenesis near the cribriform plate contributes to drainage

of CNS-derived antigens and immune cells. Nat Commun. 2019;10:229.
12. Reardon DA, Turner S, Peters KB, et al. A review of VEGF/VEGFR-targeted therapeutics for recurrent glioblastoma. JNCCN J Natl Compr Cancer Netw. 2011;9(4):414–427.
13. Iliff JJ, Wang M, Liao Y, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. Sci Transl Med. 2012; 4 (147):147ra111.
    - **This paper restarted the examination of fluid flow in the brain by identifying a new fluid flow pathway in the paravascular space called the "glymphatic system". Since its publication its function and disruption has been implicated in numerous neurological conditions and it is closely connected to the movement of interstitial fluid within the brain.**
14. Del Bigio MR. Ependymal cells: biology and pathology. Acta Neuropathol. 2010;119(1):55–73.
15. Ding T, Gu F, Fu L, et al. Aquaporin-4 in glioma invasion and an analysis of molecular mechanisms. J Clin Neurosci. 2010;17(11):1359–1361.
16. Kingsmore KM, Vaccari A, Abler D, et al. MRI analysis to map interstitial flow in the brain tumor microenvironment. APL Bioeng. 2018;2(3):031905.