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Not all mouse blood-brain barriers are created equal

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See the article by Genovesi et al in this issue, pp. 732–742.

Medulloblastoma, the most common malignant brain tumor in childhood, remains a significant contributor to morbidity and mortality in the pediatric cancer population. Our current understanding of medulloblastoma is that there are four distinct molecular subgroups: wingless (WNT), sonic hedgehog (SHH), group 3, and group 4. Moreover, each subgroup can be further stratified into more refined subgroups.[1–5]

Despite an increased understanding of the molecular subgroups of medulloblastoma, the treatment has remained mostly the same, radiation and chemotherapy. Novel targeted therapies have yet to prolong survival or lessen the significant morbidity from treatment.[6] The reason for this failure is multifactorial, but a significant roadblock to developing novel therapeutics into clinically significant treatments has been the role of the blood-brain barrier (BBB) in preventing drug penetration to tumor. In fact, the differences of the BBB in the molecular subgroups, including the decreased "tightness" of the BBB in the WNT subgroup of medulloblastoma, is a proposed mechanism for the significantly improved survival of this subgroup.[7]

Even with the importance of the BBB in medulloblastoma, there is a paucity of effective in vitro models recapitulating the true three-dimensional in vivo environment of pediatric brain tumors. A commonly used in vitro system involves using a Transwell insert and co-culturing of astrocytes, endothelial cells, and pericytes to recreate a BBB in the dish.[8] While informative, this method simplifies the BBB and while useful in certain situations, likely is not robust enough or representative enough for pre-clinical drug testing. Advances in bioengineering and biopolymer technology has allowed for the development of microfluidic devices which allow for more dynamic fluid flow through a PDMS chip with small channels lined with human endothelial cells.[9] These devices are improvements over static Transwell systems in evaluating "real-life" blood flow conditions, but still lack the complexity of the "true" microenvironment. These systems are useful in their ability to be compartmentalized, which allows the chip to have various cell types in different sections of the chip to allow for interactions of these cell populations in a dynamic environment.[10] An emerging and promising model of in vitro modeling are BBB organoids. BBB organoids utilize a combination of cells which are involved in the in vivo BBB, including endothelial cells, pericytes, and astrocytes, co-cultured together in mass (as opposed to on separate surfaces in the Transwell system) to create a more representative example of a BBB. This system is useful for its ability to detect novel therapeutics ability to penetrate the organoid system as a corollary to the ability to penetrate the intact human BBB.[11] What none of these models accurately demonstrate, is the BBB in a tumor, which likely is different than that of a non-tumor BBB.

To evaluate the tumor environment, pre-clinical testing of novel therapeutics for medulloblastoma relies on genetically engineered mouse models (GEMM). These models have proven powerful tools for understanding the development of medulloblastoma, but unfortunately, not all molecular subgroups are represented by GEMM therefore limiting its ability of pre-clinical testing for all types of human medulloblastoma. Patient-derived orthotopic xenografts (PDOX), implanting tumor from a human patient into an immune-compromised mouse brain, has allowed for more heterogeneity in models of medulloblastoma. This has permitted more molecular subgroup-specific testing of novel therapeutics and has therefore been an important addition to pre-clinical testing.[12] The authors of "Patient-derived orthotopic xenograft models of medulloblastoma lack a functional blood brain barrier" effectively show that GEMM and PDOX are not created equal when evaluating the integrity of the BBB.[13] The authors demonstrate by utilizing dynamic contrast enhancement magnetic resonance imaging and microscopic immunofluorescence that there are distinct differences in the BBB of GEMM and PDOX, even within similar genetic subgroups. The authors are persuasive at making the status of the BBB an essential consideration in review of effectiveness of new therapeutics which

have utilized these murine models. It further illustrates the importance of a diversity of experiments prior to translating a novel treatment to clinical trials.

While Genovesi et al. successfully demonstrate the differences of the BBB in these models, we are still left with the question, which model better demonstrates what happens in human medulloblastoma? As previously described, we know in the WNT subgroup, survival may be tied directly to the lack of a tight BBB. Is it possible that utilizing this knowledge, we can develop treatments that convert the tight BBB into a leaky one, allowing treatments to be more effective?Therefore, this paper illustrates the need to further investigate the BBB in human medulloblastoma in vivo. Two examples of how this may be accomplished is through phase 0 study designs and/or through novel imaging techniques. It is by increasing knowledge of the complex BBB of medulloblastoma that the odds of translating breakthroughs for medulloblastoma increase.

Conflict of interest statement. This text is the sole product of the authors and that no third party had input or gave support to its writing.

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