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The brain microenvironment: friend or foe for metastatic tumor cells?

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See the article by Kim et al, on pages 1585–1598.

Brain metastases continue to be challenging targets for therapy and prevention. One reason is that many chemotherapeutics that work well on systemic metastases have much less, if any, activity in the brain, which makes it a "sanctuary site" for solid tumors.[1] The reason for this phenomenon is much debated. Historically, it was widely assumed that the blood-brain barrier (BBB) was the most important factor in helping tumor cells escape systemic therapies. Indeed, the specific anatomical and molecular constitution of the BBB prevents sufficient access of many molecules to the (healthy) brain. Specialized endothelial cells connected by tight junctions, the vascular basement membrane, pericytes, astrocytic foot processes, and specialized transporter systems strictly regulate extravasation, while active exclusion mechanisms (eg, glycoprotein P [P-gp], breast cancer resistance protein [BCRP], and the family of multidrug-resistance proteins) exclude xenobiotics effectively.[2] However, it is also clear that the majority of brain macrometastases experience breakdown of the BBB, although to a varying extent.[3] As a result, highly variable tumor levels have been reported for different chemotherapeutic agents in clinical specimens.[4] Taken together with clinical reports of activity of primary chemotherapy in non–small lung cancer brain metastasis,[5] the picture becomes obscure, and it is increasingly doubtful that only BBB issues are responsible for the reduced activity of systemic therapies in brain metastases.

Another potential resistance mechanism for metastatic tumor cells in the brain is the interaction with brain resident cells. The brain metastatic process depends on perpetuation of a perivascular niche, at least during the early stages,[6] and this niche has been associated with promotion and/or maintenance of a stem-like and resistant cellular phenotype per se in brain tumors.[7] Again, the components of the BBB come into play; endothelial cells, pericytes, astrocytic foot processes, and/or the vascular basement membrane[8] are the most likely candidates for providing this supportive niche for cancer cells. On the other hand, the high inefficiency of the brain metastatic process (with 95%–99% of brain-arrested cancer cells failing to grow into a macrometastasis[6]) raises the question whether some of these components are more foe than friend for extravasating cancer cells in the brain. For example, a recent report suggested that astrocyte-produced plasminogen activator forces brain metastatic cancer cells into apoptosis and therefore has to be inhibited by cancer cells to survive this brain-protective mechanism.[9]

In this issue of *Neuro-Oncology*, Isaiah Fidler et al continue to picture a different role for astrocytes, adding to their previous reports on how astrocytes can help cancer cells withstand the deleterious effects of chemotherapy. First, assuming a connexin 43 gap junction-mediated, direct protective buffering of increased calcium concentrations in melanoma cells,[10] they found a gap junction-dependent upregulation of survival genes (*GSTA5*, *BCL2L1*, and *TWIST1*) that correlated with chemoresistance in lung and breast cancer cell lines.[11] In the current article, they provide further insights into the molecular mechanisms and how to potentially target them, supporting previous reports of involvement of the endothelin axis in chemoprotection.[12] In cell culture experiments, astrocyte-derived endothelin isoforms activate their receptors on cancer cells and lead to increased survival gene expression via the AKT and MAPK pathways. In turn, cancer cells secrete IL-6 and IL-8 after gap junction coupling with astrocytes to increase endothelin expression in those astrocytes. These data suggest a complex, reciprocal cross talk between the 2 cell types. Both endothelin receptors (ETAR and ETBR) are required to fully exert these interactions and mediate chemoprotection of cancer cells by astrocytes. The Food and Drug Administration- and European Medicines Agency-approved drug macitentan, used for treating pulmonary hypertension, inhibits both ETAR and ETBR and consequently shows the best single-agent activity against astrocyte-dependent protection from chemotherapy in their in vitro system. Again, Fidler et al find a striking dependency on functional gap junctions to mediate these effects. The molecular mechanisms remain to be clarified; the known differences in how (connexin 43-) gap junctions allow penetration of molecules of different sizes and chemical compositions should be helpful in future experiments addressing this question. Finally, Fidler et al demonstrate that astrocytes and also brain endothelial cells (clearly another crucial member of the vascular niche/the BBB), but neither fibroblasts nor microglia cells, are capable of mediating protective effects to cancer cells, which enhances our ability to estimate the best cellular targets for brain metastasis prevention and therapy.

It is likely that further studies, such as that by Fidler et al in this issue, will significantly increase our knowledge base for improved targeting of cancer cells in the brain, overcoming their treatment resistance, and will clarify whether there are differences between primary and metastatic brain tumors. The exploration of the complex world of interactions within the foreign, but potentially still

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helpful, soil in brain metastasis will also add important information to the increasing body of evidence that tumors are not just a group of mutated, aberrantly dividing cells, but rather entities that exploit many noncancer cells as "conspirators" to help the tumor grow and survive adverse events.

There are some caveats. First, astrocytes might play different roles under different conditions, as discussed above. Second, similarly conflicting data have been reported for the anti- versus pro-tumor effects of brain microglia, possibly depending on their activation state. Third, gap junction-mediated intercellular communication has been shown by some authors to confer chemoresistance (as in this article by Fidler et al), but other groups have found the opposite in different tumor models, including CNS malignancies.[13,14] All of these issues underscore the absolute necessity to further characterize the chemoprotective versus chemosensitizing effects of brain resident cells for cancer cells, be it via the endothelin pathway, gap junction intercellular communication, or other pathways. This must include the use of good preclinical animal models that—even if opposing effects from different cell types and/or cellular activation states exist—will finally show us the net effects regarding modulation of chemoresistance in the live brain for different disease stages and tumor types. Finally, another question is whether the potentially protective effects of brain resident cells are limited to chemotherapy. Gap junction-mediated intercellular communication between astrocytes has been demonstrated to make them resistant to the deleterious effects of reactive oxygen species,[15] thus providing a hint that astrocytes might also be capable of protecting cancer cells from the adverse events of radiotherapy.

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