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Will mastering ferroptosis allow treating refractory meningiomas?

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See Bao et al, this issue (pp. 2014–2027).

Meningiomas are the most frequent primary tumors of the central nervous system. They are thought to derive from meningothelial cells of the arachnoidal layer. They make up around 30% of CNS tumors and affect approximately 1% of the population. The great majority of meningiomas are benign, slow-growing neoplasms whereas atypical and malignant meningiomas WHO grades II and III, occurring in around 10%-15% and 1%-3%, respectively, show infiltrative growth, an increasingly high mitotic rate, and recur after resection.[1] If meningiomas require treatment, microneurosurgical resection is the mainstay of therapy, combined or replaced by radiation therapy or radiosurgery in atypical, malignant, and recurrent meningiomas—these therapies can be repeated in case of further recurrence(s), until a point where a new attempt of resection or radiation therapy will bear more risk than benefit. There is still an unmet clinical need for systemic therapy for so-called refractory meningioma.

So far, despite many efforts, systemic drug therapy against refractory meningioma does not offer effective drug regimens. Neither cytostatic drugs such as hydroxyurea, temozolomide, irinotecan, various drug combinations using cyclophosphamide/adriamycin/vincristine, cytokines like interferon-alpha, hormones like mifepristone or somatostatin analogs, targeted drugs like gefitinib, erlotinib, or sunitinib, nor antibodies like bevacizumab have yielded convincing results.[2] A recent randomized phase II trial comparing the sea squirt-derived alkaloid trabectedin against physician´s choice failed to show a significant therapeutic effect, but increased toxicity of trabectedin as compared to mostly antiangiogenic interventions.[3] In 2017, a Japanese group identified by drug screening the nucleoside analog gemcitabine as highly effective against an established cell line of malignant meningioma HKBMM and in a cell line of a patient with atypical meningioma. They also showed the effectivity of gemcitabine in vivo in a xenograft experiment with nude mice.[4] So far, only a case report reporting compassionate use of gemcitabine in 3 patients with refractory meningiomas with good tolerance and reasonably long progression-free survival has acted on this suggestion.[5]

Ferroptosis was identified a decade ago as an iron-dependent form of programmed cell death induced by the accumulation of intracellular lipid reactive oxygen species (ROS).[6] Ferroptosis occurs during many physiological processes, with remodeling of tissues such as diabetes, arteriosclerosis, acute kidney injury, degenerative CNS disease, ischemia-reperfusion injury, or antiviral immune response.[7] It is tightly regulated and these mechanisms are increasingly understood. Systematic investigations identified 2 components protecting cells from ferroptosis, eg, the systemc x_c^- cysteine/glutamate antiporter, mediating the transmembrane transport of extracellular L-cysteine and intracellular L-glutamate and the selenium-containing enzyme glutathione peroxidase (GPX4) as well as erastin, a small molecule capable of initiating ferroptosis and RSL3, an inhibitor of glutathione peroxidase 4, resulting also in ferroptosis induction.[8] Moreover, it could be shown that epithelial cells grown in high density or as spheres mediated by E-cadherin mediated cell-cell contact are able to survive GPX4 knockout, which leads to ferroptosis, thus implicating a protecting effect of E-cadherin. So far, ferroptosis is explored in many directions, from its potential physiological functions in immune function, as tumor suppressor, as radiation sensitizer, and as a promising tool in tumor therapy, allowing to eliminate selectively cells with activated RAF-MEK-ERK pathway or p53 mutation.[9] Ferroptosis ultimately leads to excessive formation of lipid peroxides and ROS, but the mechanisms of cell death due to ferroptosis are still unknown, whether cell membranes collapse and form pores or if the fluidity of membranes is affected and leads to stiffening.

In this issue, Bao et al[10] report on the induction of ferroptosis in cell lines of malignant meningioma by silencing an important transcription factor, myocyte enhancer factor 2 (MEF2C) leading to the downregulation of neurofibromatosis 2 protein (NF2) and E-cadherin. They showed in a series of 35 clinical samples that the expression of MEF2C decreases with increasing behavior of malignancy and described a positive correlation between MEF2C expression and GPX4 expression and a negative correlation to the

expression of Acyl Coenzyme A synthetase long-chain family member 4 protein expression (ACSL4), an important contributor to ferroptosis. Using 2 established meningioma cell lines, one NF2-intact, IOMM-Lee and one NF2-mutant, CH-157, and a patient-derived NF2-mutant cell line PM3, they could show that silencing MEF2C by siRNAs downregulated NF2 and E-cadherin. Exposure of these cells to 6 μM erastin triggered ferroptosis, as shown by LDH release of the cells. This was more prominent in the 2 NF2-mutant cell lines, eg, CH-157 and PM3 as compared to IOMM-Lee. Finally, they were able to confirm the role of MEF2C mediation of ferroptosis in orthotopic xenografts in nude mice.

These results constitute an important step in bringing this new concept to safe application in neuro-oncological context. They support that better understanding of the mechanisms regulating ferroptosis will allow developing new, safe therapeutic strategies against refractory meningioma. And hopefully also against the most malignant primary CNS tumor, glioblastoma.

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References

1. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. *Neuro Oncol.* 2021;23(8):1231–1251.
2. Le Rhun E, Taillibert S, Chamberlain MC. Systemic therapy for recurrent meningioma. *Expert Rev Neurother.* 2016;16(8):889–901.
3. Preusser M, Silvani A, Le Rhun E, et al. Trabectedin for recurrent WHO grade II or III meningioma: a randomized phase II study of the EORTC Brain Tumor Group (EORTC-1320-BTG) (submitted).
4. Takeda H, Okada M, Kuramoto K, et al. Antitumor activity of gemcitabine against high-grade meningioma in vitro and in vivo. *Oncotarget.* 2017;8(53):90996–91008.
5. Khaddar S, Bhelekar A, Dale O, Varghese L, Patil VM. Gemcitabine in recurrent meningioma. *South Asian J Cancer.* 2020;9(4):261.
6. Dixon SJ, Lemberg KM, Lamprecht MR, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. *Cell.* 2012;149(5):1060–1072.
7. Hao S, Liang B, Huang Q, et al. Metabolic networks in ferroptosis. *Oncol Lett.* 2018;15(4):5405–5411.
8. Yang WS, SriRamaratnam R, Welsch ME, et al. Regulation of ferroptotic cancer cell death by GPX4. *Cell.* 2014;156(1–2):317–331.
9. Jiang X, Stockwell BR, Conrad M. Ferroptosis: mechanisms, biology and role in disease. *Nat Rev Mol Cell Biol.* 2021;22(4):266–282.
10. Bao Z, Hua L, Ye Y, et al. MEF2C silencing downregulates NF2 and E-cadherin and enhances Erastin-induced ferroptosis in meningioma. *Neuro Oncol.* 2021;23(12):2014–2027.