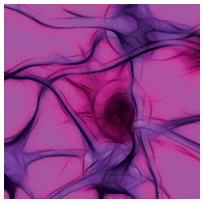
## Targeted Therapy

**Major Finding:** MRgFUS-delivered trastuzumab demonstrated safety and efficacy in treating brain metastases.

**Concept:** A first-in-human study of non-invasive MRgFUS-mediated antibody delivery revealed increased uptake.

**Impact:** This study indicates promise of MRgFUS in delivering therapeutics across the blood–brain barrier.

### MRgFUS-MEDIATED ANTIBODY DELIVERY IMPROVES DRUG UPTAKE ACROSS THE BBB



The blood–brain barrier (BBB) is a major obstacle to the delivery of therapeutics to the brain. Magnetic resonance–guided focused ultrasound (MRgFUS) is a technology developed to get around this limitation, providing a noninvasive and spatially precise way of increasing drug delivery across the BBB. It provides a temporary window of access that resolves in 24 hours and has demonstrated promise in preclinical models, but its successful use in humans has yet to be shown. Meng and colleagues used this technique along with the existing regimen for delivery of trastuzumab to four patients with HER2-positive breast cancer and brain metastases. Outpatient procedures of 20 treatments were administered with safety as the primary outcome. No serious adverse events were noted, and patients were generally released from the hospital 2 hours after treatment. Evaluation of efficacy using a radiotracer indicated that MRgFUS-treated lesions increased binding and uptake over control lesions. Furthermore, tumors were either decreased in size or stable as compared to baseline as indicated by a follow-up MRI, with three of the four patients observed showing a decrease in unidimensional tumor measurements after several months. This technique shows multiple advantages over other brain drug delivery approaches, including spatial and temporal control allowing for the specific targeting of regions of the brain that typically are not easily accessed by radiation or surgery and an ability to be combined with other anticancer therapies. This study presents first-in-human evidence of antibody delivery across the BBB using MRgFUS and implicates the use of this technology in the future treatment of other neuro-oncological and neurologic disorders. ■

*Meng Y, Reilly RM, Pezo RC, Trudeau M, Sahgal A, Singnurkar A, et al. MR-guided focused ultrasound enhances delivery of trastuzumab to Her2-positive brain metastases. Sci Transl Med 2021;13:eabj4011.*

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## Epigenetics

**Major Finding:** DNA methylation alterations facilitate cellular stress response and intratumoral heterogeneity.

**Concept:** Single-cell profiles determined epigenetic heterogeneity and its contribution to tumor evolution.

**Impact:** This study highlights the role of epigenetic heterogeneity in the adaptive stress response and therapeutic outcomes.

### EPIGENETIC HETEROGENEITY CONTROLS GLIOMA CELL STATE AND STRESS RESPONSE

Diffuse gliomas are the most common brain tumor in adults and continue to be incurable. This is largely due to these tumors exhibiting inter- and intratumoral heterogeneity, which contributes to therapeutic resistance, and is further complicated by cellular plasticity which allows cells to transiently move between states in response to different stimuli. This process has been shown to controlled, in part, through epigenetic modifications, including DNA methylation (DNAme). However, the specific epigenetic mechanisms that regulate this cellular plasticity and tumor heterogeneity in glioma remain poorly understood. Johnson, Anderson, and colleagues analyzed single-cell DNA methylomics, single-cell transcriptomics, and single-cell copy number profiles along with bulk genetic profiles from 11 glioma patient samples to dissect the heterogeneous nature of tumor cell populations. Increased disorder of DNA methylation was associated with epigenetic heterogeneity, with higher levels of disorder supporting epigenetic remodeling. This phenotype was observed at regions that are critical for gene regulation, and the perturbation of epigenetic control by DNAme disorder promoted the adoption of epigenetic states that allowed tumor cells to respond to stress stimuli including hypoxia and therapeutics. Conversely, environmental stress, through either hypoxia or radiation-induced DNAme disorder, as well as genetic stimuli such as somatic copy number alterations and aneuploidy-related replication stress also shifted the cellular state of glioma cells. Furthermore, DNA methylation changes that supported these shifts and response to stress were recurrently selected, and enhancement of DNA methylation disorder was associated with accelerated disease progression, with more aggressive tumors exhibiting increased local DNA methylation disorder. This study was able to define epigenetic states that contribute to glioma evolution as well as provide insight into the source of intratumoral heterogeneity that fuels this disease. ■

*Johnson KC, Anderson KJ, Courtois ET, Gujar AD, Barthel FP, Varn FS, et al. Single-cell multimodal glioma analyses identify epigenetic regulators of cellular plasticity and environmental stress response. Nat Genet 2021;53:1456–68.*

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