Glioblastoma cells assemble to a syncytial communicating network based on tumor microtubes (TMs) as ultra-long membrane protrusions. The relationship between network architecture and transcriptional profile remains poorly investigated. Drugs that interfere within this syncytial connectivity such as meclofenamate (MFA) may be highly attractive for glioblastoma therapy.

Methods: In a human neocortical slice model using glioblastoma cell populations of different transcriptional signatures, three-dimensional tumor networks were reconstructed and TM-based intercellular connectivity was mapped on the base of two-photon imaging data. MFA was used to modulate morphological and functional connectivity; downstream effects of MFA treatment were investigated by RNA sequencing and fluorescence-activated cell sorting (FACS) analysis.

Results: TM-based network morphology strongly differed between the transcriptional cellular subtypes of glioblastoma and was dependent on axon guidance molecule expression. MFA revealed both a functional and morphological demolishment of glioblastoma network architectures which was reflected by a reduction of TM-mediated intercellular cytosolic traffic as well as a breakdown of TM length. RNA sequencing confirmed a downregulation of NCAM and axon guidance molecule signaling upon MFA treatment. Loss of glioblastoma communicating networks was accompanied by a failure in the upregulation of genes that are required for DNA repair in response to TMZ-treatment and culminated in profound treatment response to TMZ-mediated toxicity.

Conclusion: The capacity of TM formation reflects transcriptional cellular heterogeneity. MFA effectively demolishes functional and morphological TM-based syncytial network architectures. These findings might pave the way to a clinical implementation of MFA as a TM-targeted therapeutic approach [1)].

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Human and mouse breast and lung cancer cells express protocadherin 7 (PCDH7), which promotes the assembly of carcinoma-astrocyte gap junctions composed of connexin 43 (Cx43). Once engaged with the astrocyte gap-junctional network, brain metastatic cancer cells use these channels to transfer the second messenger cGAMP to astrocytes, activating the STING pathway and production of inflammatory cytokines such as interferon-α (IFNα) and tumor necrosis factor (TNF). As paracrine signals, these factors activate the STAT1 and NF-κB pathways in brain metastatic cells, thereby supporting tumour growth and chemoresistance. The orally bioavailable modulators of gap junctions meclofenamate and tonabersat break this paracrine loop, and we provide proof-of-principle that these drugs could be used to treat established brain metastases [2)].

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Schneider M, Vollmer L, Potthoff AL, Ravi VM, Evert BO, Rahman MA, Sarowar S, Kueckelhaus J, Will P, Zurhorst D, Joseph K, Maier JP, Neidert N, d'Errico P, Meyer-Luehmann M, Hofmann UG, Dolf A, Salomoni P, Güresir E, Enger PØ, Chekenya M, Pietsch T, Schuss P, Schnell O, Westhoff MA, Beck J, Vatter H, Waha A, Herrlinger U, Heiland DH. Meclofenamate causes loss of cellular tethering and decoupling of functional networks in glioblastoma. Neuro Oncol. 2021 Apr 17:noab092. doi: 10.1093/neuonc/noab092. Epub ahead of print. PMID: 33864086.
2)
Chen Q, Boire A, Jin X, Valiente M, Er EE, Lopez-Soto A, Jacob LS, Patwa R, Shah H, Xu K, Cross JR, Massagué J. Carcinoma-astrocyte gap junctions promote brain metastases by cGAMP transfer. Nature. 2016 May 18;533(7604):493-8. doi: 10.1038/nature18268. PubMed PMID: 27225120; PubMed Central PMCID: PMC5021195.