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New targets in the glioblastoma tumor microtube multiverse: Emerging roles for the TGF-β/TSP1 signaling axis

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Tumor microtubes play a critical and increasingly recognized role in facilitating the diffuse invasion and therapy resistance that characterizes glioblastoma multiforme (GBM). Tumor microtubes are ultra-long, cytoskeletal-enriched membrane tubes that bridge tumor cells into a functional syncytium and penetrate the brain at the invasive front.[1] Several seminal studies revealed that tumor microtubes and their associated networks meaningfully contribute to chemoresistance, radioresistance, and malignant repopulation of surgical resection cavities.[1,2] Tumor microtubes are also strongly associated with the stem-like compartment of astrocytic gliomas and participate in the neuron-glioma synapse.[3–5] Existing evidence supports that tumor microtubes rely on neurodevelopmental and cytoskeletal pathways, but mechanistic insights beyond select signaling networks are limited.[1,6–8]

In the recent *Neuro-Oncology* publication "TGF-ß promotes microtube formation in glioblastoma through thrombospondin 1," Joseph et al present evidence that TGF-ß signaling promotes and enhances the formation of tumor microtubes in a subset of IDH wild-type GBM.[9] The study builds upon previous work demonstrating that astrocytic gliomas (both IDH wild-type and IDH-mutated) abundantly exhibit tumor microtubes, while tumor microtube formation in the less aggressive oligodendrogliomas (IDH-mutated; 1p/19q co-deleted) is rare.[1] Joseph et al analyzed published TCGA expression datasets and found TGF-ß expression in IDH wild-type GBMs is upregulated in comparison with IDH-mutated and 1p/19q co-deleted oligodendrogliomas. This finding is in line with previous evidence demonstrating that TGF-ß is a driver of leading-edge invasion in GBM tumors and the genomic location of *TGFB1* on human chromosome 19q further supports TGF-ß is a potential tumor microtube target.[10]

Joseph et al go on to employ pharmaceutical and genetic approaches to interrogate TGF-ß signaling in 3 patient-derived models of IDH wild-type GBM in vitro, ex vivo, and in in vivo orthotopic xenograft mouse models. In 2 of the 3 tested models, they observed that TGF-ß stimulation enhanced tumor microtube formation above baseline, while TGF-ß inhibition prevented tumor microtube enhancement in response to TGF-ß stimulation. They further demonstrate that the enhancement in tumor microtube formation in these 2 models is achieved through SMAD2/3-mediated activation of thrombospondin 1 (TSP1). These findings are rigorous and significant, particularly given current understanding of tumor microtube pathobiology is very limited.

The evidence put forth in this study also importantly proposes that tumor microtube formation can result from multiple signaling pathways and highlights how little is understood about tumor microtube diversity. Evidence of this can be found in the third IDH wild-type model that formed tumor microtubes but did not exhibit tumor microtube enhancement nor diminution in response to manipulation of TGF-ß signaling. This observation elaborates upon Jung et al's proposal that multiple intratumoral subgroups of tumor microtubes likely underly the observed diversity in tumor microtube function[3] and suggests that tumor microtubes also exhibit intertumoral diversity. Future studies are needed to interrogate additional pathways that influence tumor microtube formation and to define if differences in tumor microtube signaling confers differences in tumor microtube function.

Collectively, this study offers compelling evidence that the TGF-ß/SMAD/TSP1 signaling axis is a potential target for tempering pro-invasive tumor microtube networks in a subset of aggressive gliomas. It will be interesting for future studies to expand and probe the interactome of this novel signaling aggregate for targeted development of anti-tumor microtube therapies that may ultimately function beyond this specific tumor cohort. Productive clinical partnerships and utilization of live cell glioma biobanks will be needed to clearly define and identify the subset of clinical cases that will benefit from such therapies.

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