Glioblastoma cells vampirize WNT from neurons and trigger a JNK/MMP signaling loop that enhances glioblastoma progression and neurodegeneration

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Glioblastoma (GB) is the most lethal brain tumor and Wingless-related-integration-site (WNT) pathway activation in these tumors is associated with a poor prognosis. Clinically the disease is characterized by progressive neurological deficits. However, whether these symptoms result from direct or indirect damage to neurons is still unresolved. Using *Drosophila* and primary xenografts as models of human GB, we describe a mechanism that leads to activation of WNT signaling [Wingless (Wg) in *Drosophila*] in tumor cells. GB cells display a network of tumor microtubes (TMs) that enwrap neurons,

accumulate Wg receptor Frizzled1 (Fz1), and, thereby, deplete Wg from neurons, causing neurodegeneration. We have defined this process as “vampirization”. Furthermore, GB cells establish a positive feedback loop to promote their expansion, where the Wg pathway activates cJun N-terminal kinase (JNK) in GB cells, and in turn JNK signaling leads to the post-transcriptional upregulation and accumulation of matrix metalloproteinases (MMPs), which facilitate TMs infiltration throughout the brain, TMs network expansion and further Wg depletion from neurons. Consequently, GB cells proliferate due to the activation of the Wg-signaling target, β-catenin, and neurons degenerate due to Wg signaling extinction. Our findings reveal a molecular mechanism for TMs production, infiltration and maintenance that can explain both neuron-dependent tumor progression and also the neural decay associated with GB.