Introduction

Glioblastomas create an immunosuppressive microenvironment partly via tumor-associated macrophages (TAMs) that secrete osteopontin (SPP1). Osteopontin is a glycoprotein that binds the CD44 receptor on T cells and other cells, acting as an **“immune checkpoint”** that blunts T cell activation​[pmc.ncbi.nlm.nih.gov](https://pmc.ncbi.nlm.nih.gov/articles/PMC10956315/#:~:text=To%20elucidate%20the%20mechanisms%20of,Additionally)​[pmc.ncbi.nlm.nih.gov](https://pmc.ncbi.nlm.nih.gov/articles/PMC10956315/#:~:text=,PMC%20free%20article). In both adult and pediatric gliomas, a subset of TAMs with high SPP1 expression (often termed **TAM-SPP1**) is linked to impaired T cell responses and poor patient outcomes​[pmc.ncbi.nlm.nih.gov](https://pmc.ncbi.nlm.nih.gov/articles/PMC10956315/#:~:text=SPP1%20demonstrated%20a%20significant%20association,dataset%2C%20two%20distinct%20molecular%20subtypes)​[pmc.ncbi.nlm.nih.gov](https://pmc.ncbi.nlm.nih.gov/articles/PMC10956315/#:~:text=consist%20of%20brain,2h). The SPP1–CD44 interaction on T cells inhibits their proliferation and promotes early exhaustion, allowing the tumor to evade immune attack​[pmc.ncbi.nlm.nih.gov](https://pmc.ncbi.nlm.nih.gov/articles/PMC10956315/#:~:text=To%20elucidate%20the%20mechanisms%20of,Additionally)​[pmc.ncbi.nlm.nih.gov](https://pmc.ncbi.nlm.nih.gov/articles/PMC6264653/#:~:text=authors%20demonstrate%20that%20downregulation%20of,to%20immune%20checkpoint%20inhibitor%20therapy). Notably, disrupting this axis is an emerging strategy in immunotherapy – **osteopontin is now recognized as an immune-suppressive pathway** whose blockade could reinvigorate T cells and improve responses to checkpoint inhibitors​[pmc.ncbi.nlm.nih.gov](https://pmc.ncbi.nlm.nih.gov/articles/PMC6264653/#:~:text=authors%20demonstrate%20that%20downregulation%20of,to%20immune%20checkpoint%20inhibitor%20therapy). Beyond immunosuppression, osteopontin/CD44 signaling in glioblastoma also promotes tumor aggressiveness: it maintains stem cell–like traits and radiation resistance in glioma cells within the perivascular niche​[pmc.ncbi.nlm.nih.gov](https://pmc.ncbi.nlm.nih.gov/articles/PMC3999042/#:~:text=radiation%20resistance,like). This dual role makes the SPP1–CD44 axis a compelling therapeutic target in glioblastoma.