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COMMENTARY

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Targeting gliomas with STAT3-silencing nanoparticles

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ABSTRACT

Glioblastoma is an aggressive brain tumor with poor prognosis. The brain is protected by the blood–brain barrier, which precludes transport of chemotherapeutics. We developed nanoparticles that achieve delivery of small-interfering RNA against Stat3 after systemic administration. Nanoparticles combined with radiation inhibited tumor progression and elicited anti-glioblastoma immunity in mice.

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Commentary

Glioblastoma (GBM) is a primary malignant brain tumor that is poorly differentiated, and mostly inaccessible to total surgical resection.[1,2] Prognosis and survival of patients affected by GBM remain virtually unchanged in spite of advances in surgery, radiation, and chemotherapy.[1,2] Also, the brain is protected by the blood–brain barrier, which precludes efficient delivery of chemotherapeutics and renders most cancer drugs ineffective.[1,2] Although clinical implementation of biodegradable polymer wafers has established safety to release anti-cancer drugs in the tumor, there has only been modest increases in patient median survival.[3] One major disadvantage of this therapeutic approach is that it requires repeated invasive intracranial administration of the drug, highlighting the need for effective systemic therapies. Progress in brain tumor therapy has been hampered by the lack of adequate delivery methods to the brain, particularly for small molecule drugs.[4] Signal and Transducer of Activation 3 (Stat3) transcription factor has been discovered to be a hub for multiple signaling pathways which mediate tumor progression and immune functions.[4–7] Histopathological analysis of brain tumors demonstrated Stat3 to be overexpressed in 53% of patients with grade III astrocytomas and grade IV GBMs, but not in patients with lower-grade tumors.[7] Stat3 levels have also been shown to be negatively associated with median survival.[7] In a recent study, we identified potent inhibition of tumor growth and increased cell death in GBM cells after treatment with several Stat3 inhibitors.[4] Intriguingly, Stat3 inhibition using small molecules resulted in regression of GBMs growing in the flank of mice, but not in intracranial tumors.[4] While this work validates Stat3 as a powerful clinical target, it also underscores the need for effective delivery strategies of anti-Stat3 therapeutics to the brain.

Nanoparticles (NPs) of a varying composition have emerged as promising drug-delivery platforms over the years.[8] Recently we developed and systemically administered 200 nm albumin-based-NP formulation to treat GBM bearing mice.[9] Our electrohydrodynamic system is a new NP synthesis technology that can produce albumin-based NPs with distinct compartments.[8] In this system the rapid solvent evaporation induces nanoprecipitation resulting in particles with distinct compartments. By modulating the matrix polymer, we can independently set the modes of drug delivery. Therefore, our technology enables control over not only dose ratios, but also timing of delivery, offering significant advantages over standard use of the so-called bystander effect.[8] Additionally, we adapted the tumor-penetrating peptide iRGD to our NP formulation,[10] to promote the entry and diffusion of small-interfering RNA (siRNA) against Stat3 (Stat3*i*) within the GBM microenvironment.[8] We demonstrated that iRGD-targeted Stat3*i*-NPs are able to penetrate the blood–brain barrier and accumulate in the brain of intracranial GBM bearing mice after systemic delivery.[8] Intracellular uptake of NPs by GBM cells in the tumor microenvironment resulted in effective silencing of Stat3 expression in the tumor cells.[8] We also assessed the efficacy of Stat3*i*-NP and observed significant extension in the median survival of GBM bearing mice.[8] Combining Stat3*i*-NP treatment with the standard of care, i.e., ionizing radiation (IR) resulted in tumor regression and long-term survival in 87.5% GBM bearing mice.[8] Strikingly, when long-term survivors were rechallenged with GBM in the contralateral hemisphere, without further treatment, we observed 100% survival, indicating the development of anti-GBM immunological memory.[8] The neuropathological analysis of the brains from tumor-rechallenged long-term survivors showed complete tumor regression and did not reveal signs of neurotoxicity or overt inflammation.[8] Levels of cellular components of the blood in complete blood cell counts analysis for animals receiving NP treatment compared with control animals were within the normal range.[8] Furthermore, the levels of enzymes involved in

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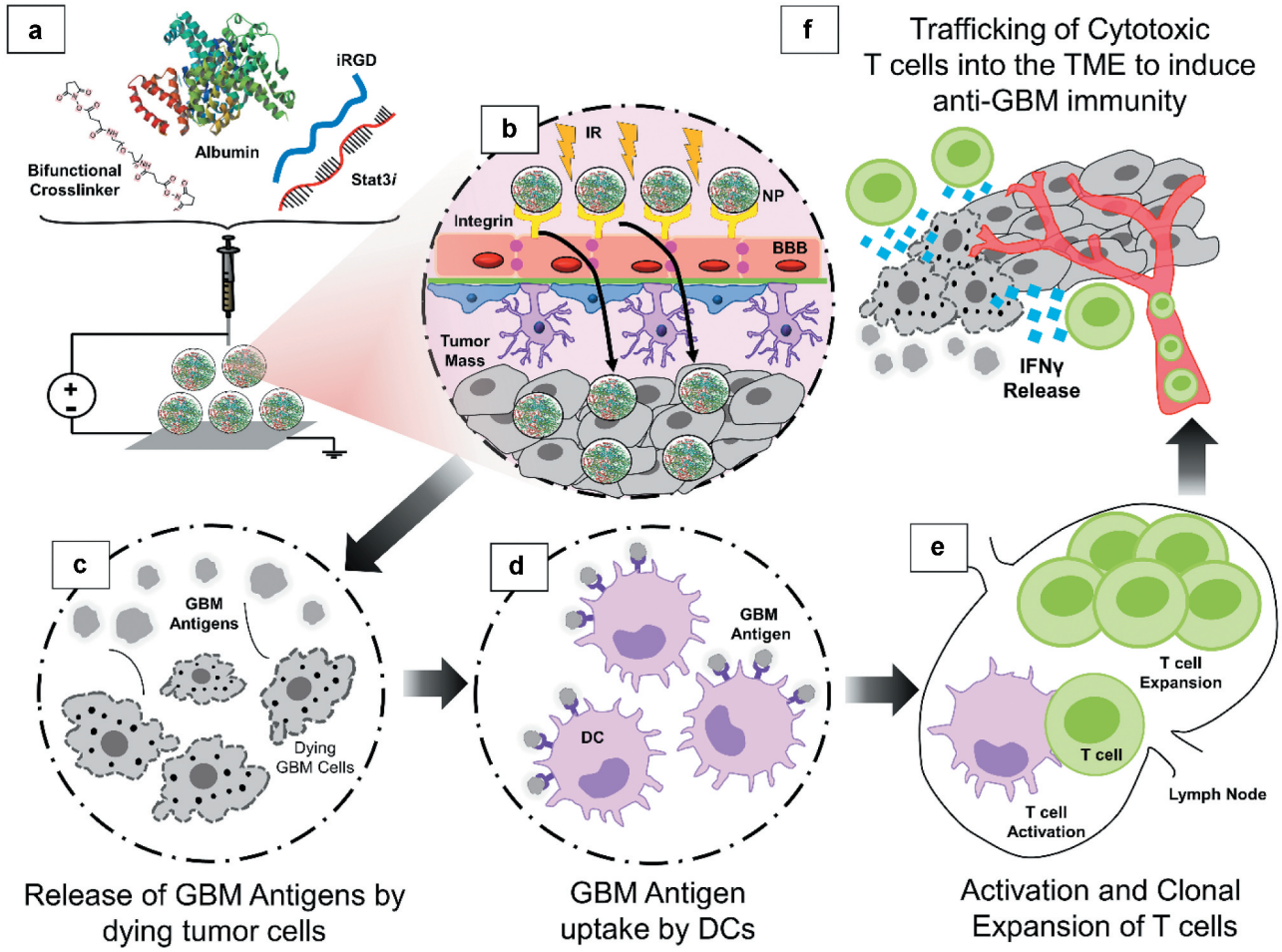

Figure 1. Immunological mechanism targeting Glioblastoma (GBM) upon Signal and Transducer of Activation 3 (Stat3) downregulation with nanoparticles (NPs). (a) Electrodynamic co-jetting of 200 nM Stat3 small-interfering RNA (Stat3*i*) containing NPs. Jetting formulation consists of bifunctional crosslinker, albumin, iRGD (tumor-targeting peptide) and Stat3*i*. (b) Systemic delivery of STAT3 siRNA NPs in combination with radiation (IR). The iRGD peptide binds to the integrins on the blood–brain barrier and GBM cells promoting the entry of Stat3*i* into the tumor cells by transcytosis. (c) Dying GBM cells release antigens into the tumor microenvironment (TME). (d) Dendritic cells (DCs) in the TME become activated upon encountering GBM antigens. (e) DCs uptake and process the GBM antigens and migrate to the lymph nodes, where they present antigens to CD8 T cells and mediate the activation and clonal expansion of T cells. (f) Cytotoxic T cells traffic to the GBM TME to kill the remaining tumor cells and promote anti-GBM immunity.

kidney (creatinine, blood urea nitrogen) and liver (aminotransferase, aspartate aminotransferase) physiology for animals receiving NP treatment compared with animals in control group remained normal, indicating that no overt adverse side-effects occurred in the liver and renal systems.[8] These data suggest that NP treatment do not cause off-target systemic toxicity within the brain tumor microenvironment and peripheral organs.

Overall, our results demonstrate that Stat3*i*-NPs in combination with IR targets distinct mechanisms to elicit immunogenic cell death of GBM cells, triggering anti-GBM immunity, inducing immunological memory against recurring GBM.[8] Stat3 signaling in conjunction with IL-6/JAK signaling has been shown to drive tumor invasiveness while suppressing anti-tumor immunity.[4–6] Therapeutic agents that target IL-6/JAK/Stat3 have been shown to stimulate anti-tumor immunity, thus, inhibiting Stat3 signaling in glioma will be therapeutically beneficial.[4–6]

In summary, our study demonstrates the development of a novel therapeutic systemic delivery platform for GBM, i.e., albumin-based tumor-targeting NPs, which could be suitable for clinical translation (Figure 1). The information gleaned from our study will allow for the delivery of powerful anti-tumor drugs at the target site while sparing healthy tissue. Our NP system can serve as a precision therapeutic platform that can cross the blood–brain barrier, deliver the drug payload into the GBM, and concentrate the drug with the tumor microenvironment, thus mediating tumor regression and anti-brain tumor immunity. The findings from our work could also be broadened to metastatic cancers to the brain, e.g., melanoma and breast as well as other solid cancers. Clinically our therapeutic strategy will likely lead to improved patient survival, inhibit brain cancer progression, and prevent tumor relapse. Overall, the results from this study exhibit high translational potential and will have direct implications in the development of novel therapies for primary and metastatic brain tumor patients.

Disclosure of potential conflicts of interest

The University of Michigan has filed a patent application (US 62/931512) on materials related to the work described in this auto-commentary.

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