but had no effect as monotherapy. It is, therefore, not surprising that a recent phase II clinical study investigating the effect of PLX3397 in patients with recurrent GBM in the absence of radiation did not show improvement in progression-free survival. The drug was, however, well tolerated and demonstrated to readily cross the blood–brain barrier.

Radiation therapy has been shown to enhance the invasiveness of glioma cells and microglia play a critical role in glioma cell invasion. Indeed, the CSF-1R inhibitor PLX3397 has been shown to potently inhibit glioma spread in an orthotopic murine model of glioma. Thus, CSF-1R inhibitors may act by a third mechanism to improve radiation therapy that is by inhibiting radiation-induced GBM invasiveness.

Interestingly, the CSF-1R inhibitor PLX647 has been shown to sensitize tumors to T cell checkpoint blockade in a mouse model of melanoma. PLX647 monotherapy blocked tumor-infiltrating myeloid-derived suppressor cells and enhanced the antitumor T cell responses, resulting in delayed tumor growth with a modest benefit on survival. However, in combination with T cell checkpoint blockade (α-CTLA4 and α-PD1), PLX647 resulted in significantly prolonged survival compared to either treatment alone. These results suggest that CSF-1R inhibitors also may enhance the beneficial radiation-induced immune response directed towards the tumor, thereby improving radiation therapy by yet another mechanism.

In summary, CSF-1R inhibitors may act on 4 different levels to enhance the therapeutic effects of radiation on brain tumors and mitigate radiation-induced side effects. These inhibitors are well tolerated, and importantly, cross the blood–brain barrier. Thus, future clinical trials combining radiation therapy with CSF-1R inhibitors are warranted to evaluate these 4 potential mechanisms in GBM patients. CSF-1R inhibitors in combination with radiation may be a powerful approach to improve the dismal prognosis and reduce the devastating neurotoxicity associated with GBM treatment today.

From the Bottom Up: The Role of Sacral Pattern Generators in Modulating Rostral Lumbar Flexor Motor Neurons

Spinal central pattern generators (CPGs) are crucial for producing the rhythmic output needed for motor control of stepping and stabilizing the body axis during movement. It has become increasingly clear that these CPGs are under both supraspinal and intraspinal control. The discovery of ascending sacral central pattern generators (SCPGs) has become enticing, as it would suggest that in cases where supraspinal and descending control may be lost, such as stroke or spinal cord injury, reactivation of these CPGs may be effective in re-establishing important motor functions.

In this well planned and written manuscript, Cherniak et al demonstrate the roles of SCPGs in modulating lumbar flexor motor neurons in an in vitro spinal cord preparation of newborn rodents. These authors have previously shown the existence of an important SCPG that is activated by the α1-adrenoreceptor agonist methoxamine (METH), and this work elucidates the circuitry and pathways involved in this ascending pathway. They show that sacral METH can produce locomotor-like rhythmic output of lumbar motor neurons and that it is the ventral SCPG at the level of S1 or S2 that is necessary and sufficient for such responses. Furthermore, it appears that these sacral CPGs communicate with the rostral lumbar motor neurons through ventral funiculus neurons (VFNs). Using an elegant combination of calcium signaling and in vitro electrophysiology, they are able to show that METH induces rhythmic discharges in sacral VFNs, which have both crossed and uncrossed connections to the lumbar motor neurons. Using their results, the authors posit a model for sacral control
of lumbar motor neurons, involving both crossed and uncrossed connections and stimulating and inhibiting connections, which are crucial for the rhythmic patterns of stepping (Figure).

These findings are enticing in that they show that caudal CPGs can elicit the same rhythmic lumbar outputs that supraspinal and descending pathways usually control. A major limitation of this work is that it is done all in vitro and it would be crucial to show the role of these ascending pathways in live, freely moving animals. If indeed, these ascending pathways are capable of eliciting such patterned behavior such as stepping, then these circuits may be an important outlet where electrical and biochemical inputs are plugged into in cases where supraspinal and descending pathways are damaged, such as stroke and spinal cord injury.

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