Mohyeldin et al. have studied the role of hypoxia-inducible erythropoietin (EPO) signaling in the growth, invasiveness, and response of human astrocytomas and other cancers to cisplatin chemotherapy. They have shown that EPO and its receptor (EPOR) are upregulated in high-grade gliomas as opposed to low-grade gliomas. Interestingly, upregulation is perhaps most intense at regions of pseudopalisading cells surrounding necrotic foci. Although the EPOR gene promoter does not have a hypoxia response element, which would help explain its upregulation in the context of hypoxic conditions, the authors suggest that upregulation of EPO per se following hypoxia may be sufficient to increase EPOR levels.

The ability of hypoxia to potentiate EPO reversal of cisplatin toxicity is very interesting. The authors suggest that these effects may be the result of activation of bcl-2 and bcl-XL expression in the JAK-STAT (Janus kinase–signal transducers and activators of transcription) pathway, and this could be easily assessed. However, could there be some other way in which EPO inactivates cisplatin toxicity based on the known mechanism of action of cisplatin? Did the authors examine other chemotherapeutic agents to see if EPO attenuates their toxicity?

The authors have shown that EPO promotes the invasiveness of several glioma cell lines in vitro and EPOR genetically manipulated U251 glioma cells in vivo. The use of the latter model borders on applications of upcoming technologies to limit the growth of human gliomas based on hypoxia-inducible EPO signaling. The authors used a truncated EPOR mutant to stably transfect U251 cells. They showed that this transfected mutant cell line has reduced abilities to invade and grow in subcutaneous spaces in athymic mice. Confirmatory studies involving the use of small inhibitory (si)RNAs directed against either EPO or full-length EPOR would have been complementary to their data. In addition, it would have been interesting if the authors had placed their xenografts into the intracranial compartment rather than the subcutaneous compartment. Then, we may have witnessed whether the true invasive process that characterizes human astrocytomas was recapitulated in their model.

This work stimulates us to consider the generation of antagonists to hypoxia-inducible EPO signaling to decrease the growth and invasiveness of human astrocytomas. Undoubtedly, these agents will be forthcoming as either small pharmaceutical inhibitors or direct antagonists in the near future. I congratulate the authors on their work.

RESPONSE: Dr. Rutka asks: “could there be some other way in which EPO inactivates cisplatin toxicity based on the known mechanism of action of cisplatin? Did the authors examine other chemotherapeutic agents to see if EPO attenuates their toxicity?” We have not yet finished examining the effect of EPO in blocking the cytotoxic actions of other chemotherapy agents. We focused on cisplatin because, in previous studies, several investigators have shown that EPO could prevent cisplatin-induced nephrotoxicity. However, other researchers have shown that exogenous EPO increases melanoma resistance to hypoxic stress and that pretreatment of melanoma cells with EPO significantly increased resistance to dacarbazine treatment. Moreover, EPO increased the phosphorylation of EPOR, RAF (mitogen-activated protein kinase [MAPK] kinase), and MEK (MAPK/extracellular signal–regulated kinase [ERK] kinase), suggesting activation of other cell stress signaling pathways.

With respect to Dr. Rutka’s suggestions concerning siRNAs and placement of xenografts in the intracranial compartment, we have not yet finished examining the effects of siRNA intervention and are currently pursuing the intracranial glioma model. We agree that research in these areas should provide important information because EPO is also made in the brain.

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References