

## Editorial

### Glioma invasion

WILLIAM T. COULDWELL, M.D., PH.D., AND V. W. YONG, PH.D.

*New York Medical College, Valhalla and New York, New York; and University of Calgary, Alberta, Canada*

A characteristic pathological feature of malignant glioma cells is their ability to extensively invade surrounding brain parenchyma—particularly along white matter tracts—thus rendering focal therapies incapable of controlling tumor growth and resulting in inevitable recurrence. In this regard, identification of factors responsible for such invasion has become a central theme in glioma research, and elucidation of intracellular signal transduction systems and regulatory mechanisms important for controlling the process of invasion are of great clinical interest.

In the article by Kubiakowski, et al., in this issue (Kubiakowski T, Jang T, Lachyankar MB, et al: Association of increased phosphatidylinositol 3-kinase signaling with increased invasiveness and gelatinase activity in malignant gliomas. *J Neurosurg* 95:480–488, September, 2001), the authors have demonstrated that increased phosphatidylinositol 3-kinase (PI3-K) activity correlates with Akt phosphorylation and also increased matrix metalloproteinase (MMP)-2 and -9 production. Matrix metalloproteinases are fundamentally involved with proteolytic degradation of the extracellular matrix (gelatin), a preliminary step in the invasion process.<sup>6</sup> The increased MMP-2/-9 production associated with PI3-K activity correlates with invasion through matrigel, as demonstrated in this study. Pharmacological inhibition of PI3-K activity by Wortmannin and LY294002 decreases invasion of glioma cells, suggesting that targeting of this pathway is of potential therapeutic importance.

Issues from this work that remain to be resolved include the following: 1) whether observations on the C6 established glioma cell line in rodents can be extended to human gliomas, and, particularly, gliomas in vivo. The authors should continue the present investigation to examine human tumors (both established and low passage lines) in tissue culture and study the effects of the inhibitors in vivo for further preclinical evaluation. 2) Does reintroduction of PTEN expression by gene transfer techniques alone normalize the upregulated PI3-kinase activity and hence

MMP-modulated invasion? The answer to this important question would help to clarify whether clinical gene therapy approaches to express PTEN in glioma cells that have lost this tumor suppressor gene would result in decreased MMP expression. The PI3-K activity may also likely be driven by upstream activators, as in the interaction of integrins with the extracellular matrix of white matter growth factors<sup>3</sup> (for example, scatter factor/hepatocyte growth factor) that regulate motility and MMP production<sup>2</sup> or other signaling cascades, such as protein kinase C (PKC).<sup>5</sup> 3) How do PI3-kinase activation and Akt phosphorylation lead to MMP expression? Phosphatidylinositol is the precursor of several intracellular signal transduction systems, but we do not know whether the decreased invasiveness of the C6 cells in this study is related to Akt-mediated signal transduction directly or indirectly through activation of other kinases such as mitogen-activated protein kinases (MAPKs). 4) Does PI3-kinase/Akt also control other MMPs whose contribution to glioma invasiveness may be more important than that of the gelatinases (MMP-2/-9) (for example, membrane type 1-MMP).<sup>1,4</sup>

The authors are to be commended for the present observations that extend our knowledge of the complex interplay of intracellular events that result in increased invasion, which pose yet another potential target for treating these devastating tumors.

#### References

1. Belien AT, Paganetti PA, Schwab ME: Membrane-type 1 matrix metalloprotease (MT1-MMP) enables invasive migration of glioma cells in central nervous system white matter. *J Cell Biol* 144:373–384, 1999
2. Bowers DC, Fan S, Walter KA, et al: Scatter factor/hepatocyte growth factor protects against cytotoxic death in human glioblastoma via phosphatidylinositol 3-kinase- and AKT-dependent pathways. *Cancer Res* 60:4277–4283, 2000
3. Keely PJ, Westwick JK, Whitehead IP, et al: Cdc42 and Rac1 induce integrin-mediated cell motility and invasiveness through PI(3)K. *Nature* 390:632–636, 1997

4. Nakada M, Kita D, Futami K, et al: Roles of membrane type 1 matrix metalloproteinase and tissue inhibitor of metalloproteinases 2 in invasion and dissemination of human malignant glioma. **J Neurosurg** **94**:464–473, 2001
5. Uhm JH, Dooley NP, Villemure JG, et al: Glioma invasion in vitro: regulation by matrix metalloproteinase-2 and protein kinase C. **Clin Exp Metastasis** **14**:421–433, 1996
6. Uhm JH, Dooley NP, Villemure JG, et al: Mechanisms of glioma invasion: role of matrix-metalloproteinases. **Can J Neurol Sci** **24**:3–15, 1997

RESPONSE: We appreciate Drs. Couldwell and Yong's comments regarding our paper. As they point out, much work remains to be done to understand completely the relationship underlying glioma invasion. Our paper begins to characterize one of many pathways that are involved in this complex tumor behavior.

Perhaps the most important criticism made by Drs.

Couldwell and Yong relates to whether our observations on the rat C6 glioma cell line can be extended to human gliomas. This criticism is appropriate when trying to extrapolate any observation made in animals to the clinical situation. We have therefore begun follow-up studies in which we assess human glioma tissues obtained during surgery by using immunohistochemistry for the colocalization of phosphorylated Akt and MMPs.

Last, we agree that the ultimate goal of such studies is the establishment of new therapeutic strategies for this very difficult clinical problem.

N. S. LITOFSKY, M.D.

TAICHANG JANG, PH.D.

ALONZO H. ROSS, PH.D.

LAWRENCE D. RECHT, M.D.

University of Massachusetts Medical Center  
Worcester, Massachusetts