Editorial

Designing New Drugs For High Grade Gliomas

Fighting against cancer has variable results, depending on the tumour type. Major improvements have been achieved during the past three decades for breast, prostate and colorectal cancer. In many cases, patients with those diagnoses can actually be cured, or at second best, live in hopes that their cancer may have become a manageable disease, accompanied by a decent quality of life. The story is different with high grade gliomas. Notwithstanding the virtual absence of metastases, these tumours still represent a formidable challenge to oncologists. High grade gliomas widely infiltrate normal brain, so as complete surgical removal is almost impossible and residual malignant tissues are refractory to eradication by conventional therapies. Even with today's best tripartite treatment approach (surgery + radiation + chemotherapy), survival benefit for patients with GBM is limited. After initial shrinkage, tumour relapse is a nearly inevitable re-appearing specter that takes away patients' lives within a few months.

Why are residual glioma tissues so prone to drive tumour recurrence and progression? Importantly, recent findings indicate that resistant cell populations escaping radio- and chemotherapy often exhibit stem cell features. In particular, these glioma stem cells (GSC) express a number of proteins that are typical of stemness and are able to differentiate towards astrocyte, neuron or oligodendrocyte phenotypes. Whether GSC derive from transformation of normal neural stem cells (NSC) or de-differentiation of tumoral cells still is an open question that yet does not prevent us from exploiting their peculiarities for specific targeting. Recent work has shown that at least six resistance mechanisms are active in glioma. Hence, we have to simultaneously target most, if not all of them if we want to eradicate the tumour, a staggering task!. This issue of Current Pharmaceuticals Design deals with current novel approaches to overcome resistance to therapies in high grade gliomas.

GSC share with normal NSC common developmental signaling pathways involving a number of pluripotency transcription factors and microRNAs. Hence, overcoming GSC resistance may likely increase neurotoxicity due to damage on normal stem and progenitor cells. David Hsieh [1] discusses how the stem phenotype is maintained in GSC in comparison to NSC as well as the pathogenic mechanisms linked to stem factors in the tumour-driving cells, two important issues for development of GSC-specific and relatively non-toxic drugs.

John M. Heddleston and coworkers [2] address the role of the microenvironment in maintenance of GSC phenotype. GSC are often detected in vascularized and hypoxic niches and several factors produced by the perivascular environment, including nitric oxide and some surface molecules or matrix components such as integrins and laminins may feed the GSC tumourigenic phenotype. Hypoxic conditions favour GSC maintenance through promotion of Wnt/β-catenin signaling and acidic conditions have been proposed as well to contribute to GSC-driven malignant progression. The tumour microenvironment is a possible target of therapies aimed to eradicate glioma-driving cells.

Ghazaleh Tabatabai and coworkers [3] review preclinical and clinical data on integrins inhibition as a possible therapeutic approach in malignant gliomas. Integrins are a large family of cell surface receptors that mediate the interaction of glioma cells with their microenvironment thus modulating the invasive properties of the tumour. Integrin inhibition by Cilengitide, a cyclic inhibitor binding to the arginine-glycine-aspartic acid (RGD) ligand-binding motif on alphaVbeta3 and alphaVbeta5 integrin receptors is in advanced clinical development and a phase III randomized clinical trial of Cilengitide plus conventional radio- and chemotherapy in GBM patients is ongoing (CENTRIC trial, EORTC26071-22072).

The Akt protein is a nodal downstream effector of the RTK/PTEN/PI3K pathway whose deregulation contributes to uncontrolled glioma cell proliferation. Akt is often activated by phosphorylation in GBM tumours where it participates in amplification of growth signals, suppression of apoptosis and tumour progression. Kelli McDowell and coworkers [4] discuss AKT as a possible target for development of novel drugs against glioma progression. A number of AKT inhibitors have been developed and have shown therapeutic properties in animal studies, although none of them has so far advanced to the clinical setting.

Mitochondrial malfunctions have been associated with progression of brain tumours. Glioma cells which rely on glycolytic metabolism often adapt to energetic stress by modifying mitochondrial metabolism. Corinne E. Griguer and Claudia R. Oliva [5] deal with those mitochondrial alterations that in some cases have been related to development of a multidrug-resistance (MDR) phenotype in gliomas. In particular, the Electron Transporter Chain (ETC) complexes belonging to the family of ATP-binding cassette (ABC) transporters may play a role in the development of chemoresistance in glioma. This aspect will have to be taken into account for development of more effective therapies.

Moderate activity of the endoplasmic reticulum (ER) stress response protects cells from limited insults thus contributing to chemoresistance. Enhanced ER stress response observed under more severe conditions yet triggers apoptosis. In glioma cells, the ER stress response is continuously engaged due to various chronic stress conditions (e.g. hypoxia, hypoglycemia, acidification) and therefore possibly unable to protect tumoural cells from additional attacks. Axel H. Schönthal and coworkers [6] propose to challenge the ER stress response in glioma cells until it becomes apoptotic, in order to improve therapies. Current pharmacological interventions and combination strategies designed to that aim are discussed.

Immunotherapy is an additional weapon, which may cooperate with standard therapy to eliminate residual brain tumour disease. In their contribution, Antonio Daga and coworkers [7] discuss how the identification of glioma-associated antigens and immune escape mechanisms may allow to improve immunotherapy protocols. In particular the review deals with active immunotherapy, which consists in the activation of the patient's immune system against GBM through the use of vaccines, toll-like-receptor agonists and/or cytokines. Additional approaches include the adoptive trasfer of in vitro generated effector cells or the use of monoclonal antibodies as such, or for drug or isotope delivery. Several of these approaches have shown promising results in pre-clinical GBM models. Other immunotherapies are currently evaluated in clinical trials and some of them showed potential clinical benefit, supporting further clinical testing.

Sabina Berezowska and Jürgen Schlegel [8] review in the last article current therapeutic advances targeting ErbB receptors. The ErbB growth factor receptor family includes four types of tyrosine kinases which are recognized as key signalling pathways in gliomas. In particular, a truncated, constitutively activated variant form of epidermal growth factor receptor (EGFR) named EGFR variant III (EGFRvIII) is associated with poor survival in GBM. Some anti-ErbB therapeutics including monoclonal antibodies (e.g. cetuximab) and small molecule tyrosine kinase inhibitors (e.g. gefitinib, erlotinib, AEE788) have recently entered clinical trials with limited clinical efficacy so far. Deepening our understanding of ErbB biology in gliomas may pave the way to improved ErbB –based therapies in gliomas.

In conclusion, I would like to thank all the authors for their excellent contributions. These reviews provide an useful up-date of our current knowledge on glioma therapy and a perspective of future therapies, which may hopefully cooperate with actual treatments to improve clinical benefit in high-grade gliomas.

ACKNOWLEDGEMENTS

Work in author's laboratory is supported by Compagnia S. Paolo, Turin, Italy (Project "Sensibilizzare i tumori cerebrali alla radio- e chemioterapia con inibitori dei checkpoint del ciclo cellulare", Grants 2009. 1174 and 2010. 1944).

REFERENCES

[1] Hsieh, D. Collateral damage control in cancer therapy: defining the stem identity in gliomas. Curr Pharm Des 2011; 17(23): 2370-85.
[2] Heddleston JM, Hitomi M, Venere M *et al*. Glioma stem cell maintenance: the role of the microenvironment. Curr Pharm Des 2011; 17(23): 2386-401.
[3] Tabatabai G, Tonn J-C, Stupp R, Weller M. The role of integrins in glioma biology and anti-glioma therapies. Curr Pharm Des 2011; 17(23): 2402-10.
[4] McDowell KA, Riggins GJ, Gallia GL. Targeting the AKT pathway in glioblastoma. Curr Pharm Des 2011; 17(23): 2411-20.
[5] Griguer CE, Oliva CR. Bioenergetics pathways and therapeutic resistance in gliomas: emerging role of mitochondria. Curr Pharm Des 2011; 17(23): 2421-7.
[6] Schönthal AH, Chen TC, Hofman FM, Louie SG, Petasis NA. Preclinical development of novel anti-glioma drugs targeting the endoplasmic reticulum stress response. Curr Pharm Des 2011; 17(23): 2428-38.
[7] Daga A, Bottino C, Castriconi R, Gangemi R, Ferrini S. New perspectives in glioma immunotherapy. Curr Pharm Des 2011; 17(23): 2439-67.
[8] Berezowska S, Schlegel S. Targeting ErbB receptors in high-grade glioma. Curr Pharm Des 2011; 17(23): 2468-87.

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