NEOPLASIA
www.neoplasia.com

Volume 18 Number 12 December 2016 pp. 806–807 806

Precision Medicine with TGF-β Inhibition Using Tumor Explants: Comment on "Patient-Specific Screening Using High-Grade Glioma Explants to Determine Potential Radiosensitization by a TGF-β Small Molecule Inhibitor" by N. Sumru Bayin et al.

Haidong Huang*and Jennifer S. Yu*,†

*Department of Stem Cell Biology, Cleveland Clinic, Cleveland, OH, USA; †Department of Radiation Oncology, Cleveland Clinic, Cleveland, OH, USA

Abstract

In a new report, Bayin et al. described an *ex vivo* explant model to test the patient-specific response to transforming growth factor-β inhibition in high-grade gliomas.

Neoplasia (2016) 18, 806–807

In this era of precision medicine, rapid and efficient means of testing and predicting responses to therapy are urgently needed. Although platforms focusing on tumor cell intrinsic contributions to response to therapy are valuable, platforms that also take into account the microenvironment are particularly important. The microenvironment, including immune and stromal cells, and different kinds of signaling molecules, plays a key role in influencing cancer progression and response to therapy. In a new report, Bayin et al. offer a tumor explant model as a relatively simple, fast, and low-cost model to personalize treatment of transforming growth factor-β (TGF-β) inhibition for patients with high-grade glioma (HGG) [1].

The TGF-β pathway is a key regulator of cell growth, proliferation, differentiation, and apoptosis in normal development and neoplastic progression. TGF-β binds to the type II receptor (TGFBR2), which then recruits and activates the type I receptor (TGFBR1). Active TGFBR1 can initiate a signaling cascade through phosphorylating SMAD proteins or can signal through noncanonical pathways.

In HGG, TGF-β is frequently upregulated and correlates with worse patient survival [2]. TGF-β can act on both the tumor cells and microenvironment to promote proliferation and resistance to radiation, in addition to promoting angiogenesis and suppressing antitumor immune cell infiltration [3]. TGF-β is secreted by glioma stem cells to regulate their self-renewal, and TGF-β inhibition improves the radiation response and reduces survival of glioma stem cells [4–7]. Targeting TGF-β signaling, therefore, is a valuable therapeutic strategy and is currently under investigation in several clinical trials [8–11]. Because of intra- and intertumoral heterogeneity in HGG, strategies that define the subset of patients with HGG who would derive greatest benefit from TGF-β inhibition are needed.

In this report, Bayin et al. develop a tumor explant model as a relatively simple and low-cost model to test the response of TGF-β inhibition for patients with HGG. Fresh surgical specimens were diced and cultured on laminin-coated filters in the upper chamber of Transwell inserts and maintained in serum-free media. Notably, all seven tumors that were explanted were viable, demonstrating the ease in establishing this system.

Furthermore, the explants preserved tumor architecture and signaling for at least 1 week, sufficiently long to test response to the combination of TGF-β inhibition and radiotherapy *in situ*. The authors validated that TGF-β signaling was intrinsically active in all of the explants but with variable strength. Nuclear pSmad2 increased after

Address all correspondence to: Jennifer S. Yu, Department of Radiation Oncology, Department of Stem Cell Biology, Cleveland Clinic, 9500 Euclid Ave, T28, Cleveland, OH 44195, USA.
E-mail: yuj2@ccf.org
Received 22 October 2016; Revised 27 October 2016; Accepted 27 October 2016

1476-5586
http://dx.doi.org/10.1016/j.neo.2016.10.009

stimulation with TGF-β and was reduced by the TGFβRI inhibitor LY364947 (RIKI). RIKI also decreased radiation-induced γ-H2AX foci formation and reduced Sox2 expression, suggesting that DNA damage repair and, potentially, stem cell properties were dependent on TGF-β signaling.

Interestingly and importantly, the explanted tumors showed distinct responses to TGF-β inhibition and irradiation. Five of the seven explanted tumors showed reduced γ-H2AX foci formation and suppression of radiation-induced Sox2 upregulation after RIKI treatment. One explant that was not responsive to RIKI showed no significant change in γ-H2AX foci after irradiation but did show reduced Sox2 upregulation. Another explant showed no difference in γ-H2AX or Sox2. A third explant showed reduced γ-H2AX but not Sox2. These disparate responses to irradiation in the setting of TGF-β inhibition appeared to be independent of molecular subtype and initial pSMAD2 levels and highlight the utility of the explant model in predicting response to TGF-β treatment. The model could easily be expanded to test interactions between combinations of inhibitors and radiation with a relatively quick readout and serve as a valuable tool to help guide therapy for patients in a timely manner.

References

[1] Bayin NS, Ma L, Thomas C, Baitalmal R, Sure A, Fansiwala K, Bustoros M, Golfinos JG, Pacione D, Snuderl M, Zagzag D, et al (2016). Patient-specific screening using high-grade glioma explants to determine potential radiosensitization by a TGF-β small molecule inhibitor. *Neoplasia* **18**, 795–805.

[2] Bruna A, Darken RS, Rojo F, Ocana A, Penuelas S, Arias A, Paris R, Tortosa A, Mora J, and Baselga J, et al (2007). High TGFbeta-Smad activity confers poor prognosis in glioma patients and promotes cell proliferation depending on the methylation of the PDGF-B gene. *Cancer Cell* **11**, 147–160.

[3] Joseph JV, Balasubramaniyan V, Walenkamp A, and Kruyt FA (2013). TGF-beta as a therapeutic target in high grade gliomas—promises and challenges. *Biochem Pharmacol* **85**, 478–485.

[4] Hardee ME, Marciscano AE, Medina-Ramirez CM, Zagzag D, Narayana A, Lonning SM, and Barcellos-Hoff MH (2012). Resistance of glioblastoma-initiating cells to radiation mediated by the tumor microenvironment can be abolished by inhibiting transforming growth factor-beta. *Cancer Res* **72**, 4119–4129.

[5] Anido J, Saez-Borderias A, Gonzalez-Junca A, Rodon L, Folch G, Carmona MA, Prieto-Sanchez RM, Barba I, Martinez-Saez E, and Prudkin L, et al (2010). TGF-beta receptor inhibitors target the CD44(high)/Id1(high) glioma-initiating cell population in human glioblastoma. *Cancer Cell* **18**, 655–668.

[6] Penuelas S, Anido J, Prieto-Sanchez RM, Folch G, Barba I, Cuartas I, Garcia-Dorado D, Poca MA, Sahuquillo J, and Baselga J, et al (2009). TGF-beta increases glioma-initiating cell self-renewal through the induction of LIF in human glioblastoma. *Cancer Cell* **15**, 315–327.

[7] Ikushima H, Todo T, Ino Y, Takahashi M, Miyazawa K, and Miyazono K (2009). Autocrine TGF-beta signaling maintains tumorigenicity of glioma-initiating cells through Sry-related HMG-box factors. *Cell Stem Cell* **5**, 504–514.

[8] Isarna Therapeutics GmbH (2003). Phase IIb clinical trial with TGF-β2 antisense compound AP 12009 for recurrent or refractory high-grade glioma. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2003 [2000 [cited 2016 Oct 20]. Available from: https://clinicaltrials.gov/show/NCT00431561 NLM Identifier: NCT00431561].

[9] University Medical Center Groningen, Genzyme (2011). Safety and imaging study of GC1008 in glioma. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2011 [2000 [cited 2016 Oct 20]. Available from: https://clinicaltrials.gov/show/NCT01472731 NLM Identifier: NCT01472731].

[10] Eli Lilly Company (2011). A study combining LY2157299 with temozolomide-based radiochemotherapy in patients with newly diagnosed malignant glioma. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2011 [2000 [cited 2016 Oct 20]. Available from: https://clinicaltrials.gov/show/NCT01220271 NLM Identifier: NCT01220271].

[11] Eli Lilly Company, Bristol Meyer Squibb (2015). A study of galunisertib (LY2157299) in combination with nivolumab in advanced refractory solid tumors and in recurrent or refractory NSCLC, hepatocellular carcinoma, or glioblastoma. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2015 [2000 [cited 2016 Oct 20]. Available from: https://clinicaltrials.gov/show/NCT02423343 NLM Identifier: NCT02423343].