Co-targeting TGF-β and PD-L1 with radiation therapy: The Goldilocks principle

Samuel F. Bakhoum1,2 and Charles M. Rudin3,4,*
1Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New York, NY, USA
2Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA
3Druckenmiller Center for Lung Cancer Research, Memorial Sloan Kettering Cancer Center, New York, NY, USA
4Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA
*Correspondence: rudinc@mskcc.org

In the current issue of Cancer Cell, Lan et al.1 demonstrate that a bifunctional fusion protein targeting TGF-β and PD-L1 can synergize with radiation therapy to simultaneously augment tumor control and reduce normal tissue toxicity.

The potential for synergy between radiation therapy (RT) and immune checkpoint inhibitors (ICI) has been the subject of intense investigation. However, a recent phase III randomized control clinical trial (PACIFIC) shows that the addition of ICI led to increased immune-related adverse events, including increased radiation pneumonitis,2 which presents a limitation in patients with underlying conditions such as chronic obstructive pulmonary disorder or reduced lung capacity from prior resections. This highlights the clinical need to better understand the mechanistic basis for synergy between RT and ICI as well as the means to intervene to maximize tumor control while minimizing normal tissue toxicity.2,3 A key regulator of the immune and tissue response to RT is tumor-growth factor-β (TGF-β).1 Activation of TGF-β in response to RT has been proposed to suppress anti-tumor immune responses and promote normal tissue toxicity, including lung fibrosis.2,4 Importantly, activation of TGF-β signaling and associated immune suppression and normal tissue remodeling represent adaptive responses to radiation injury and repair, suggesting that this pathway might be an attractive therapeutic target in treatments that involve radioimmunotherapy.

Lan et al.1 initially sought to address whether neutralization of TGF-β signaling can be used to overcome immune suppression in otherwise immune-depleted tumors. To test this, they used a bifunctional fusion protein composed of the extracellular domain of the TGF-βRII receptor (to scavenge/trap TGF-β) fused to anti-PD-L1 IgG. This bifunctional protein, bintrafusp alfa (BA), was tested in in multiple tumor models known to be immune depleted: Lewis lung carcinoma (LLC), GL261 glioma, 4T1 triple-negative breast cancer (TNBC), and a KrasG12D/+;Trp53R172H/+;Pdx-1-Cre (KPC) model of pancreatic adenocarcinoma (PDAC). BA monotherapy significantly reduced in vivo tumor burden in PDAC tumors, and the addition of RT to BA (BART) led to significantly improved outcomes in all models tested.

The authors went on to investigate the mechanisms underlying the efficacy of BART therapy. They observed that BA treatments significantly increased CD8+ T cell infiltration in tumors that are otherwise lymphocyte depleted. There was concomitant reduction in immune-suppressive cell types, including M2-like macrophages and granulocytic myeloid-derived suppressor cells (MDSCs). Interestingly, the synergy between BA and RT extended beyond local tumor control: using bioluminescence imaging to track established lung metastases, the authors observed marked reduction in non-irradiated metastatic lesions that did not occur when treating the primary tumor with RT alone and significantly surpassed BA monotherapy treatment. Collectively, this suggests that simultaneous targeting of TGF-β and PD-L1 might systemically enhance the anti-tumor immune effects of local RT, a phenomenon known as the abscopal effect.2 A surprising consequence of BART treatment was the extension of the clinical benefit beyond tumor control. The authors observed that animals treated with BART exhibited significantly reduced pulmonary fibrosis (or scarring) compared with control-treated animals. This observation was also extended to a radiation-induced lung fibrosis (RILF) model in which radiographic evidence of fibrosis is apparent ~25 weeks after an initial dose of 15 Gy. Interestingly, while blockade of PD-L1 or scavenging of TGF-β alone did not lead to reductions in pulmonary fibrosis, their combined inhibition led to a significant reduction in normal tissue delayed toxicity and marked improvement in pulmonary function.

To gain a deeper understanding of the changes in the tissue microenvironment induced by BART, the authors performed single-cell RNA sequencing of dissociated lungs that were treated with RT or with BART as well as untreated controls. Known fibrosis-associated markers such as fibronectin and collagen were found in fibroblasts, endothelial cells, and lipofibroblasts, which also expressed elevated levels of PD-L1 and TGF-β along with M2-like macrophages. Importantly, these cells were specifically enriched in RT-treated lungs, but not BART-treated counterparts, suggesting that dual TGF-β and PD-L1 inhibition reduces pro-fibrogenic cell types, likely accounting for the increased therapeutic window for BART.

Prior to translation to human clinical trials, further work would be helpful to assess additional potential mechanisms.
of efficacy. These include the possibility that BA can directly deplete cell types from the tumor microenvironment, an observation seen with anti-CTLA4 therapy and regulatory T cells. Alternatively, as with any antibody therapy, there is a formal possibility of an antibody-dependent cellular toxicity (ADCC). Despite these mechanistic caveats, this work addresses an important unmet translational need by identifying therapeutic strategies that harness the full, yet untapped, potential of the combination of RT and ICI. Mechanistically, its elegance draws from the direct targeting of wound healing pathways that are important in tissue repair after radiation injury but are co-opted by advanced tumors to suppress radiation-induced activation of anti-tumor immunity. In normal tissues, fine-tuning the repair pathways after injury is critical to avoiding under-repair, leaving a persistent wound and unresolved inflammation, or over-repair, promoting multiple pathologies including tissue fibrosis. This work suggests that achieving optimal tumor control and widening the therapeutic window entails similar fine-tuning of inflammatory pathways: a Goldilocks effect, where the tumor is immunologically primed to increase therapeutic efficacy while minimizing the excessive reactive inflammation that paradoxically leads to reduction in anti-tumor immunity as well as long-term tissue damage.

Beyond oncology, this work also opens the potential for therapeutic intervention in other diseases, such as idiopathic pulmonary fibrosis (IPF), a lethal condition that shares some similarities to RILF. Most notably, this work is yet another example that highlights the need for means to subtly modulate—rather than completely perturb—tissue homeostasis and immune responses, a concept that is already widely accepted in other fields, such as those involved in vascular remodeling.

DECLARATION OF INTERESTS

S.F.B. owns equity in, receives compensation from, serves as a consultant for, and sits on the scientific advisory board and board of directors of Volastra Therapeutics, Inc. C.M.R. has consulted regarding oncology drug development with AbbVie, Amgen, AstraZeneca, Epizyme, Genentech/Roche, Ipsen, Jazz, Lilly, and Syros and serves on the scientific advisory boards of Bridge Medicines, Earli, and Harpoon Therapeutics.

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