Taylor & Francis
Taylor & Francis Group

AUTHOR'S VIEW

🔓 OPEN ACCESS   Ⓡ Check for updates

Activin A backs-up TGF-ß to promote regulatory T cells

Mara De Martino [ID][a], Camille Daviaud[a], and Claire Vanpouille-Box [ID][b,a]

[a]Department of Radiation Oncology, Weill Cornell Medicine, New York, NY, USA; [b]Sandra and Edward Meyer Cancer Center, New York, NY, USA

ABSTRACT

The mechanisms accountable for the infiltration of regulatory T cells into an irradiated tumor remain elusive. In our recent study, we demonstrate that activin A promotes regulatory T cells in tumors, and impairs anti-tumor immune responses induced by radiotherapy and TGF-β blockade. Dual blockade of activin A and TGF-β may be necessary to reduce regulatory T cells mediated immunosuppression driven by radiation therapy.

Radiation therapy (RT) is recognized as an ideal partner for modern immunotherapy (IT) based on its capability to modulate the immune system. However, aside its antigenic and adjuvant properties, RT is eliciting immunosuppressive signals that can jeopardize its synergism with IT. Notably, one of the major inhibitory mechanism elicited by RT is the increase infiltration of regulatory T cells (Treg) into the tumor.[1]

Transforming Growth Factor-beta (TGFβ) is a potent immunosuppressive cytokine of the tumor microenvironment (TME) that promote the conversion of naïve CD4 + T cells into CD4 + FoxP3 + T cells (Treg). TGFβ is secreted as an inactivated form in the extracellular matrix awaiting for external stimuli to unleash itself from the latency-associated peptide (LAP). Reactive oxygen species (ROS) generated by radiation therapy (RT) modify the backbone of the LAP-TGFβ complex to release the active cytokine. Consequently, the increase bioavailability of TGFβ within the TME of an irradiated tumor could be responsible for the increase representation of Treg. However, evidence challenge the role of TGFβ in Treg expansion post RT with two publications reporting no effect on Treg representation despite TGFβ inhibition in an irradiated melanoma tumor model[2] and in peripheral blood of some metastatic breast cancer patients receiving focal RT with fresolimumab, a human TGFβ blocking antibody.[3]

Activin A belongs to the TGF-β superfamily and activates the canonical SMAD2/3 pathway through its own set receptors with, namely, activin A type II (ActRIIA, ActRIIB) and type I receptors (mainly ActRIB but also ActRIA and ActRIC; aka ALK4, ALK2 and ALK7, respectively).[4] Therefore, activin A and TGFβ are sharing biological processes including (but not limited to) the induction of FoxP3 expression and the generation of Treg.[4,5] Interestingly, activin A is also overexpressed in several tumors and is increased upon RT.[6,7]

In that context, we investigated the role of activin A in the RT-induced increase in Treg in breast cancer.[8] *In vitro*, most irradiated mouse and human breast cancer cells oversecreted activin A in response to RT. Of note, we observed that irradiated breast cancer cells incubated with a pan-isoform TGFβ neutralizing monoclonal antibody further secrete activin A, therefore underscoring a potential crosstalk between these two cytokines.

Next, we focused on the consequences of activin A overexpression in cancer cells on the Treg compartment. Using two mouse breast cancer cells with different baseline of activin A, TSA (low activin A secreting cells) and 4T1 (high activin A secreting cells), we found that TGFβ blockade abrogated the conversion of naïve CD4 T cells into Treg when co-cultured with low activin A secreting TSA cells. However, this effect was not observed when high activin A secreting 4T1 co-cultures were incubated with TGFβ blockade alone. Only the dual inhibition of TGFβ and activin A (using follistatin-288, a natural activin A inhibitor), effectively prevented Treg conversion in high activin A secreting cancer cells. These findings suggest a compensatory mechanism between activin A and TGFβ to maintain the generation of Treg *in vitro*.

Further confirming this concept, *in vivo* studies conducted in syngeneic BALB/c mice bearing 4T1 or TSA tumors revealed that both activin A and TGFβ were responsible for the Treg infiltration in irradiated tumors. Most importantly, our data indicated that *Inhba* (gene encoding for activin A)-deficient 4T1 xenografts significantly improved CD8 T cell priming, reduced 4T1 tumor relapses and enhanced survival of the mice. The addition of immune checkpoint blockers (ICB; anti-PD-1 or anti-CTLA -4) led to long-lasting immunological memory in some of the irradiated mice receiving the dual blockade of activin A and TGF-β. Further underscoring the role of activin A in Treg-mediated immunosuppression in irradiated breast cancer, enforced expression of activin A in TSA cells increased Treg representation in irradiated tumors and impeded systemic anti-tumor immunity elicited by RT.

These data demonstrate that tumor-derived activin A plays a major role in the signals emitted by irradiated cancer cells, and participate in immune evasion by enhancing Treg infiltration into an irradiated tumor (Figure 1).
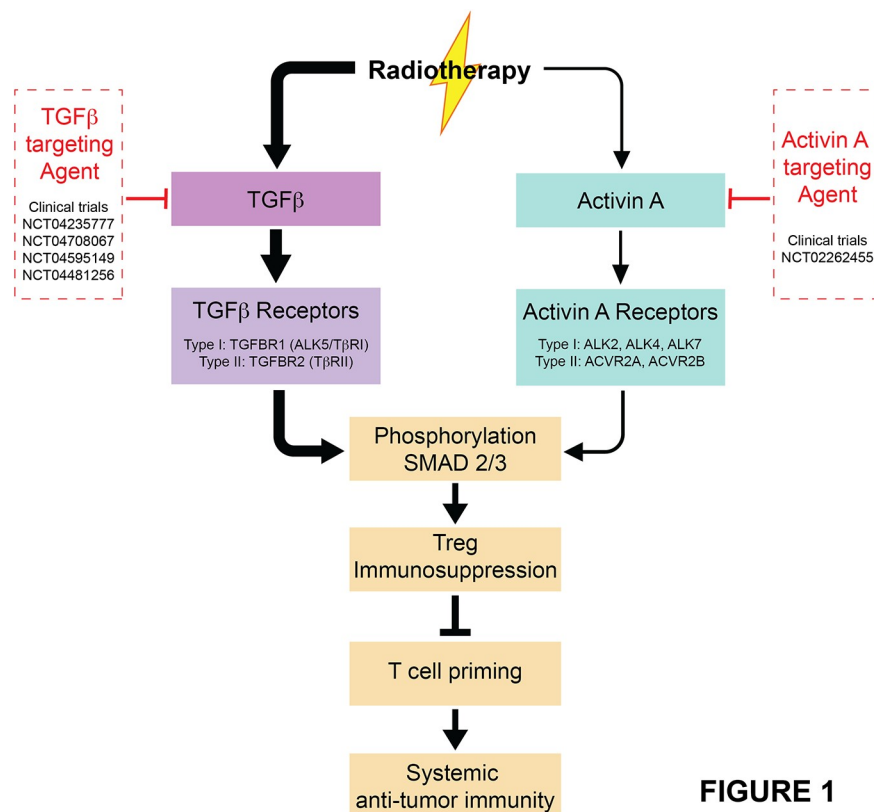

FIGURE 1

Figure 1. Activin A and TGFβ cooperate to promote Treg-mediated immunosuppression.
Tumor irradiation induces the release and activation of transforming growth factor-β (TGFβ), and can also promote the secretion of activin A. The activation of TGFβ and activin A receptors initiate intracellular signal through SMAD2 and SMAD3 to induce forkhead box P3 (Foxp3) gene transcription and the generation of regulatory T cells (Tregs). Tregs can attenuate radiotherapy-induced systemic anti-tumor immunity by inhibiting dendritic cell function and preventing T cell priming. Our findings reveal that the combination of radiotherapy with dual blockade of TGFβ and activin A reestablishes radiation-induced anti-tumor immunity and restores sensitivity to immune checkpoint blockade (ICB). In that context, ongoing clinical trials (shown in the red box) are evaluating the combination of TGFβ and ICB in irradiated tumors, while only one clinical trial is assessing the efficacy of activin A inhibition.

Bioinformatic analysis of the TCGA public database of breast cancer tumors supported our preclinical findings with a significant strong correlation between IHNBA expression, TGFB signaling and Treg representation; an observation that was independently from the breast cancer subtype.

Besides highlighting the critical role of activin A in immune escape by regulating Treg mediated immunosuppression, our findings suggest that targeting several targets may be required to improve immune activation and durable responses at least in breast cancer.

Importantly, it is intriguing to consider whether the efficacy of the phase I clinical trial testing activin A blockade in ovarian cancer[9] could be improved with the inclusion of TGFβ inhibition and/or ICB. Along similar lines, depending on the prevalence of activin A signaling in other tumor type, our work predicts for a potentially limited clinical efficacy of ongoing clinical trials assessing the combination of TGFβ and PD-L1 blockade in multiple cancer in the context of RT (NCT04481256, NCT04235777, NCT04708067, NCT04595149) in the absence of activin A blockade.

While additional studies are warranted to further explore the crosstalk between activin A and TGFβ in cancer and to validate our findings in clinic, this work shed light on a novel actionable target to enhance anti-tumor immune responses of breast cancer in the context of RT and IT.

Disclosure of potential conflicts of interest

The authors declare that they have no relevant conflict of interest.

Funding

ORCID

Mara De Martino ⓘD http://orcid.org/0000-0002-3049-6495
Claire Vanpouille-Box ⓘD http://orcid.org/0000-0001-7213-0670

References

1. Schaue D, Xie MW, Ratikan JA, McBride WH. Regulatory T cells in radiotherapeutic responses. Front Oncol. 2012;2:90. doi:10.3389/fonc.2012.00090.
2. Muroyama Y, Nirschl TR, Kochel CM, Lopez-Bujanda Z, Theodros D, Mao W, Carrera-Haro MA, Ghasemzadeh A, Marciscano AE, Velarde E, et al. Stereotactic radiotherapy increases functionally suppressive regulatory T cells in the tumor microenvironment. Cancer Immunol Res. 2017;5(11):992–1004. doi:10.1158/2326-6066.CIR-17-0040.

3. Formenti SC, Lee P, Adams S, Goldberg JD, Li X, Xie MW, Ratikan JA, Felix C, Hwang L, Faull KF, et al. Focal irradiation and systemic TGFbeta blockade in metastatic breast cancer. Clin Cancer Res. 2018;24(11):2493–2504. doi:10.1158/1078-0432.CCR-17-3322.

4. Loomans HA, Andl CD. Intertwining of activin A and TGFbeta signaling: dual roles in cancer progression and cancer cell invasion. Cancers (Basel). 2014;7(1):70–91. doi:10.3390/cancers7010070.

5. Morianos I, Papadopoulou G, Semitekolou M, Xanthou G. Activin-A in the regulation of immunity in health and disease. J Autoimmun. 2019;104:102314. doi:10.1016/j.jaut.2019.102314.

6. Carl C, Flindt A, Hartmann J, Dahlke M, Rades D, Dunst J, Lehnert H, Gieseler F, Ungefroren H. Ionizing radiation induces a motile phenotype in human carcinoma cells in vitro through hyperactivation of the TGF-beta signaling pathway. Cell Mol Life Sci. 2016;73(2):427–443. doi:10.1007/s00018-015-2003-2.

7. Staudacher JJ, Bauer J, Jana A, Tian J, Carroll T, Mancinelli G, Özden Ö, Krett N, Guzman G, Kerr D, et al. Activin signaling is an essential component of the TGF-beta induced pro-metastatic phenotype in colorectal cancer. Sci Rep. 2017;7(1):5569. doi:10.1038/s41598-017-05907-8.

8. De Martino M, Daviaud C, Diamond JM, Kraynak J, Alard A, Formenti SC, Miller LD, Demaria S, Vanpouille-Box C. Activin A promotes regulatory T-cell-mediated immunosuppression in irradiated breast cancer. Cancer Immunol Res. 2021;9(1):89–102. doi:10.1158/2326-6066.CIR-19-0305.

9. Tao JJ, Cangemi NA, Makker V, Cadoo KA, Liu JF, Rasco DW, Navarro WH, Haqq CM, Hyman DM. First-in-human phase I study of the activin A inhibitor, STM 434, in patients with granulosa cell ovarian cancer and other advanced solid tumors. Clin Cancer Res. 2019;25(18):5458–5465. doi:10.1158/1078-0432.CCR-19-1065.