
Credit: Peter Macdiarmid/Getty

and promoted regulatory T cell expansion, which was consistent with the observed increase in $CD4^+CD25^+$ T cells in allografts of mTORi-HDL-treated recipients. Depletion of $Ly6C^{low}$ regulatory macrophages on the day of transplantation resulted in early transplant rejection despite mTORi-HDL treatment. Allograft survival could be restored in these animals by adoptive transfer of wild-type monocytes, suggesting that macrophages are required for transplant acceptance following mTORi-HDL nanoimmunotherapy.

Finally, short-term treatment with a combination of mTORi-HDL and a second nanobiologic that inhibits CD40 co-stimulation (TRAF6i-HDL) synergistically promoted organ transplant acceptance and long-term survival. Thus, this study identifies a new treatment approach that impedes myeloid cell training and co-stimulation to promote indefinite immune tolerance.

Lucy Bird

ORIGINAL ARTICLE Braza, M. S. et al. Inhibiting inflammation with myeloid cell-specific nanobiologics promotes organ transplant acceptance. *Immunity* **49**, 819–828 (2018)


Credit: S. Bradbrook/Springer Nature Limited

The authors used a variety of cell systems to examine whether the ESCRT also regulates other inflammasome effector functions. Indeed, following non-canonical inflammasome activation in mouse BMDMs, the ESCRT negatively regulated IL-1β release and further GSDMD processing by preventing the entry of K^+ that can activate the NLRP3–caspase 1 pathway. In human cells infected with *ΔsifA S.* Typhimurium, the ESCRT prevented bacterial escape into the cytosol by repairing ruptured vacuoles. Finally, the ESCRT negatively regulated IL-1β release and pyroptosis after canonical (caspase 1-dependent) inflammasome activation.

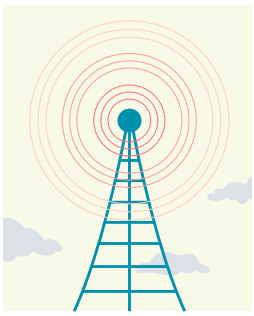
Therefore, the ESCRT machinery is recruited to GSDMD pores and is able to negatively regulate cell death and IL-1β secretion following both canonical and non-canonical inflammasome activation. The authors suggest that this activity of the ESCRT could allow cells to release a limited amount of cytokines through GSDMD pores while avoiding cell death.

Yvonne Bordon

ORIGINAL ARTICLE Rühl, S. et al. ESCRT-dependent membrane repair negatively regulates pyroptosis downstream of GSDMD activation. *Science* **362**, 956–900 (2018)

IMMUNOTHERAPY

Radiation promotes systemic responses


Credit: Lara Crow/Springer Nature Limited

Radiation therapy can enhance the systemic antitumour responses (abscopal responses) induced by anti-CTLA4 antibodies, as shown by preclinical studies. However, it was unclear how effective these induced systemic responses are against tumours unresponsive to CTLA4 blockade alone. Now, Formenti, Demaria and colleagues report in *Nature Medicine* that a combination of radiotherapy and CTLA4 blockade induced systemic antitumour T cells in patients with non-small-cell lung cancer (NSCLC) who did not respond to CTLA4 blockade alone, possibly through radiotherapy-induced upregulation of a neoantigen recognized by expanded T cell clones.

Thirty-nine patients with NSCLC whose tumours had progressed after prior systemic treatment were enrolled in a clinical trial to evaluate radiotherapy in combination with the anti-CTLA4 antibody ipilimumab. Of the 21 patients who completed the treatment, 2 patients had a complete response, 5 had a partial response and 5 had stable disease.

The authors compared levels of various soluble markers and immune cells in the tumour tissue and peripheral blood of the patients before and after treatment. Notably, radiotherapy induction of IFNβ correlated with an abscopal response to the combination therapy — in the patients who responded to treatment, serum IFNβ levels significantly increased at day 22 (after radiation therapy); those who had stable disease had a significant IFNβ increase but it was less than those who responded; and patients who progressed had no significant IFNβ increase.

Next, T cell receptor (TCR) sequencing established that several T cell clones were expanded in peripheral blood at day 22 compared with baseline in patients with complete or partial responses compared with patients with stable disease or who progressed. Furthermore, levels of IFNβ after radiotherapy combined with the changes in the TCR repertoire had the highest predictive value of response.

Examination of the tumour specificity of the expanded $CD8^+$ T cell clones in one patient with a complete response indicated that this patient had tumour-infiltrating lymphocytes that matched the expanded clones. The authors also identified two expanded T cell clones in the blood of this patient, both of which recognized a neoantigen derived from a protein thought to be upregulated during radiotherapy, karyopherin α2.

Thus, the authors hypothesize that radiotherapy may increase expression of immunogenic mutations in the tumour, leading to activation of T cells that induce IFNβ, suggesting a possible future role for a combination therapy with ipilimumab and radiotherapy.

Jordan Hindson

This article is modified from the original in *Nat. Rev. Cancer* (https://doi.org/10.1038/s41568-018-0094-4).

ORIGINAL ARTICLE Formenti, S. C. et al. Radiotherapy induces responses of lung cancer to CTLA-4 blockade. *Nat. Med.* https://doi.org/10.1038/s41591-018-0232-2 (2018)