



Liver metastases “siphon” off immunotherapy response

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For many different cancers, the advent of immunotherapy (IT) treatments, in particular immune checkpoint inhibitors, aimed at reviving the immune response against cancer cells, has led to a great improvement in terms of clinical benefit. Despite the success of IT, even in advanced metastatic cancers, some patients still fail to respond for reasons yet unclear (1,2). Yu *et al.* in an issue of *Nature Medicine*, set out to investigate whether metastatic progression to specific distant organs could systemically affect response to IT (3). The authors demonstrate that liver metastases, but not metastases to other organs, limit IT efficacy both in metastatic patients and preclinical models. The clinical significance of these findings is most relevant when considering that metastasis is the primary cancer-related cause of death, and the liver is a frequent site of metastasis (4,5) and most IT are largely restricted to patients at advanced stage of disease.

Yu *et al.* investigated the correlation between the presence of distant metastases and response to IT in several cohorts of patients. In metastatic melanoma and non-small cell lung cancer (NSCLC), the authors observed a diminished response to IT in patients with metastases to the liver, as well as worse clinical outcome in terms of overall and progression free survival, independently of other clinicopathological features including PD-L1 expression and tumor burden. Due to its physiological role, the liver is constantly exposed to antigens and is therefore characterized by a tolerant immune environment, generated by immunosuppressive mechanisms such as T cell anergy, induction of regulatory T cells, and deletion of antigen-specific T cells (6). This could reasonably be

one of the mechanisms contributing to the lack of a local responsiveness to therapy. Interestingly however, melanoma patients with liver metastases receiving IT were also shown to have increased systemic tumor burden, strongly suggesting a systemic-rather than local-effect on anti-tumor immunity. The authors further confirmed the correlation between metastatic tropism to the liver and limited therapeutic benefit from immune checkpoint blockade in a cohort of melanoma, NSCLC, urothelial and renal cancer patients, extending the relevance of these findings to a wide variety of human cancers. The tumor microenvironment has been long considered as the master regulator of antitumor immune responses, but with the advent of IT, this local view is being challenged. Cancer is a systemic disorder, perturbing the immune organization as a whole (7) and a more comprehensive picture emerges, inclusive of multiple immune cell types interacting systemically across tissues.

To unearth the mechanism underlying these variable therapeutic outcomes, the authors developed a murine model of liver metastases, where IT sensitive MC38 colorectal cancer cells were injected subcutaneously to establish the primary tumor and via intrasplenic inoculation to generate the liver metastases. Only mice harboring a primary tumor, but no concomitant liver lesions, responded to anti-PD-L1 treatment, whereas the therapeutic effect was completely abrogated in the presence of liver metastases. Results were further confirmed in a similar mouse model of lung metastases. Notably, following anti-PD-L1 treatment, primary tumors were robustly infiltrated by CD8⁺ T cells, which dropped in frequency in the presence of liver metastases. Naïve T cell priming and activation were

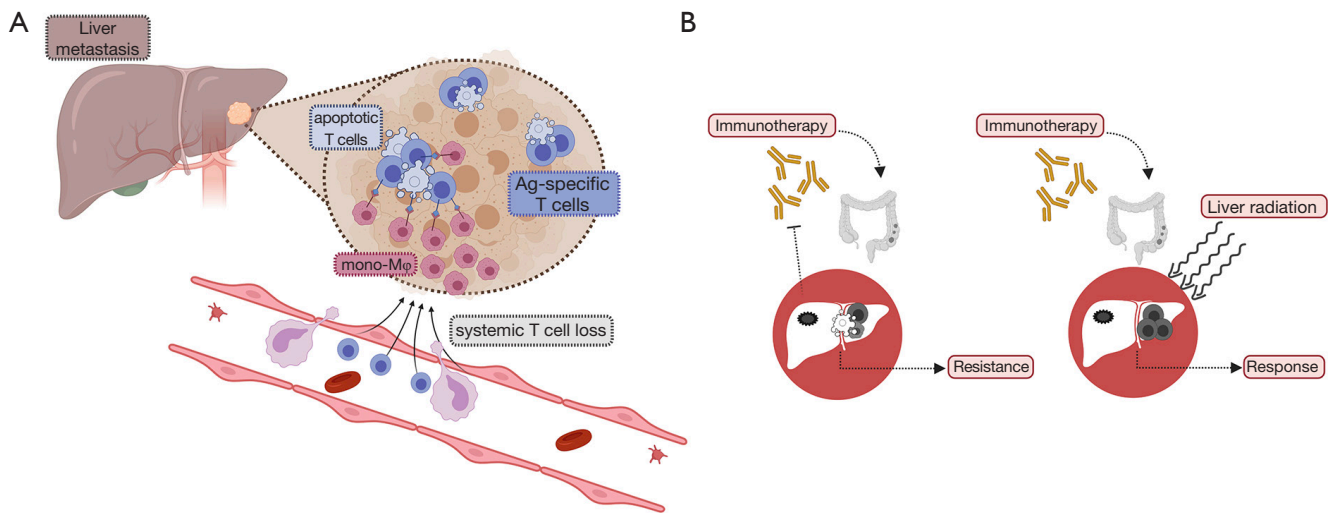


Figure 1 Macrophage-mediated T cell killing hampers systemic response to IT in liver metastases. (A) Liver metastases result in systemic T cell loss due to contact-dependent elimination of antigen-specific T cells by immunosuppressive monocyte-derived hepatic macrophages. (B) Applicability to the therapeutic setting of gastrointestinal cancers poorly responding to single-agent checkpoint inhibitors. Combination of liver radiation and IT results in response, following rewiring of the liver microenvironment. Created with BioRender.com. IT, immunotherapy.

unaffected by the presence of liver metastases, possibly suggesting that liver metastases induced a shift in antigen-specific T cell systemic distribution. Indeed, the numbers of antigen-specific CD8⁺ T cells were drastically reduced in primary tumors, draining lymph nodes and peripheral blood of mice harboring liver lesions. The relevance of these results to the human disease was confirmed by the mirrored finding that NSCLC patients with liver metastases had reduced absolute lymphocyte counts compared to patients without liver lesions. Comprehensive sequencing of primary tumors, including melanoma, NSCLC, breast, prostate, and colorectal cancer, from metastatic patients revealed diminished T cell clonality and diversity, and decreased T cell effector functions in patients with liver, but not lung, metastases.

To explain this systemic and liver metastases-dependent vanishing of anti-tumor T cells, the authors extensively evaluated the immune microenvironment of mice with hepatic lesions using flow cytometry, mass cytometry (CyTOF) and single-cell sequencing. This comprehensive approach revealed higher apoptosis and dysfunction markers in tumor antigen-specific CD8⁺ T cells in liver metastases compared to other sites including the primary tumor. The investigation of the hepatic immune microenvironment also highlighted an increase in monocyte-derived

CD11b⁺/F4/80⁺ myeloid cells, skewed towards an M2-like immunosuppressive phenotype by tumor cells; depletion of these cells rebalanced the numbers of apoptotic CD8⁺ T cells in liver lesions, ultimately restoring systemic T cell distribution and anti-PD-L1 responsiveness. Mechanistically, hepatic macrophages expressed higher levels of FasL compared to lung macrophages, and *in vitro* hepatic tumor-educated macrophages induced T cell apoptosis in a contact dependent manner via FasL-Fas interaction (Figure 1A).

Since radiotherapy is used in the clinic for hepatic tumors and is known to stimulate anti-tumor immunity, the authors next tested the therapeutic implications of their findings utilizing liver-directed radiation, alone or in combination with anti-PD-L1, to modulate the immune infiltrate in liver metastases and improve CD8⁺ T cell cytotoxicity. Radiotherapy treatment alone was able to reduce myeloid cell frequency and increase CD8⁺ T cell infiltration in hepatic lesions, ascribable to a shift from myeloid to lymphocyte-recruiting cytokine production in the liver, while the combination with IT additionally led to robust regression of tumor growth and prolonged survival compared to IT alone.

The study by Yu *et al.* identifies the tolerogenic hepatic microenvironment as a key negative modulator

of systemic IT responsiveness in metastatic patients. Specifically, the authors ascribe this phenomenon to a “siphoning” of antigen-specific CD8⁺ T cells to the liver, which are subsequently eliminated in a contact-dependent manner by immunosuppressive monocyte-derived hepatic macrophages. Ultimately, this leads to a systemic T cell “desert”, undermining IT efficacy, which greatly relies on CD8⁺ T cell infiltration. A recent study reported a similar liver metastases-dependent effect on systemic anti-tumor immunity and IT responsiveness, however mediated by a different underlying mechanism encompassing regulatory T cell recruitment and activation and modulation of CD11b⁺ monocytes at the primary tumor site (8).

The findings elucidated by this study have widespread implications, given that most tumors metastasize to the liver. Importantly, Yu *et al.* also demonstrate that liver-directed radiotherapy combined with IT may be able to restore anti-tumor immunity and responsiveness to anti-PDL1 treatment (Figure 1B). This approach could have a positive impact on many gastrointestinal cancers, which frequently metastasize to the liver, and currently respond poorly to single-agent checkpoint inhibitors (1), provided that long-term side effects of liver radiation are considered. Additionally, both anti-PD-L1 and radiotherapy treatments are already FDA approved for many cancer types, thereby possibly encouraging new clinical trials of combinatorial treatments.

Responsiveness to IT was restored by depleting hepatic myeloid cells, mostly macrophages, responsible for tumor antigen-specific T cell apoptosis. This finding further supports ongoing efforts to target macrophages, alone or in combination with checkpoint inhibitors, to limit immunosuppression behind resistance to IT (9-11). However, as also highlighted by Yu *et al.* in this work, hepatic myeloid cells are a heterogeneous population, comprising different phenotypic and functional subsets (12,13). A deeper investigation to pinpoint the macrophage subset responsible for IT refractoriness could aid in developing more effective and less toxic immunomodulatory treatments.

Collectively, this study brings to light novel mechanisms by which liver metastases hinder systemic IT efficacy and provides promising insights towards broadening immune checkpoint blockade therapeutic benefit.

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References

1. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. *Science* 2018;359:1350-5.
2. Sharma P, Hu-Lieskovan S, Wargo JA, et al. Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy. *Cell* 2017;168:707-23.
3. Yu J, Green MD, Li S, et al. Liver metastasis restrains immunotherapy efficacy via macrophage-mediated T cell elimination. *Nat Med* 2021;27:152-64.
4. Ganesh K, Massagué J. Targeting metastatic cancer. *Nat Med* 2021;27:34-44.
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020;70:7-30.
6. Krenkel O, Tacke F. Liver macrophages in tissue homeostasis and disease. *Nat Rev Immunol* 2017;17:306-21.
7. Hiam-Galvez KJ, Allen BM, Spitzer MH. Systemic immunity in cancer. *Nat Rev Cancer* 2021;21:345-59.
8. Lee JC, Mehdizadeh S, Smith J, et al. Regulatory T cell control of systemic immunity and immunotherapy response in liver metastasis. *Sci Immunol* 2020;5:eaba0759.

9. Cortese N, Donadon M, Rigamonti A, et al. Macrophages at the crossroads of anticancer strategies. *Front Biosci (Landmark Ed)* 2019;24:1271-83.
10. Mantovani A, Marchesi F, Malesci A, et al. Tumour-associated macrophages as treatment targets in oncology. *Nat Rev Clin Oncol* 2017;14:399-416.
11. Weissleder R, Pittet MJ. The expanding landscape of inflammatory cells affecting cancer therapy *Nat Biomed Eng* 2020;4:489-98.
12. Zhang Q, He Y, Luo N, et al. Landscape and Dynamics of Single Immune Cells in Hepatocellular Carcinoma. *Cell* 2019;179:829-45.
13. Ramachandran P, Dobie R, Wilson-Kanamori JR, et al. Resolving the fibrotic niche of human liver cirrhosis at single-cell level. *Nature* 2019;575:512-8.

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