

Targeting *SLC7A11* Enhances Immune Response in HCC Ablation

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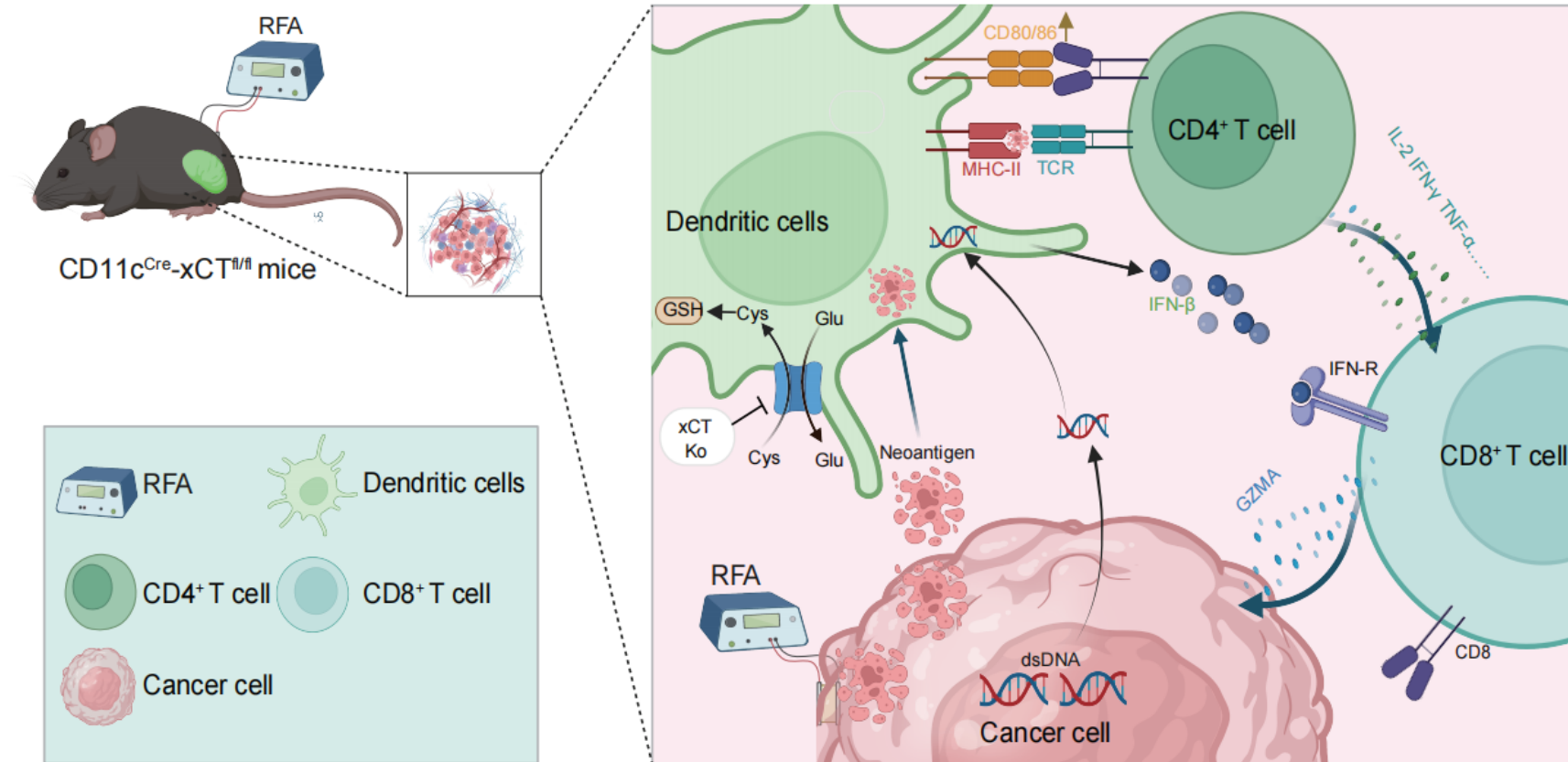
Introduction

- Radiofrequency ablation (RFA) is widely used in clinical practice as a well-established treatment for hepatocellular carcinoma (HCC). RFA often results in incomplete ablation of larger tumors, leading to a high risk of tumor recurrence.

- Dendritic cells (DCs), as the most effective antigen-presenting cells, serve as a crucial bridge between innate and adaptive immunity. In the TME, DCs can capture and process tumor antigens, presenting them to T cells and activating a specific immune response against the tumor.

- Overexpression of *SLC7A11* is associated with poor prognosis in various cancers. Here, we used comprehensive bioinformatics analyses and experimental validations to investigate *SLC7A11*'s role in the liver cancer immune microenvironment, elucidate the underlying regulatory mechanisms and offer insights on the RFA combination therapy model for HCC.

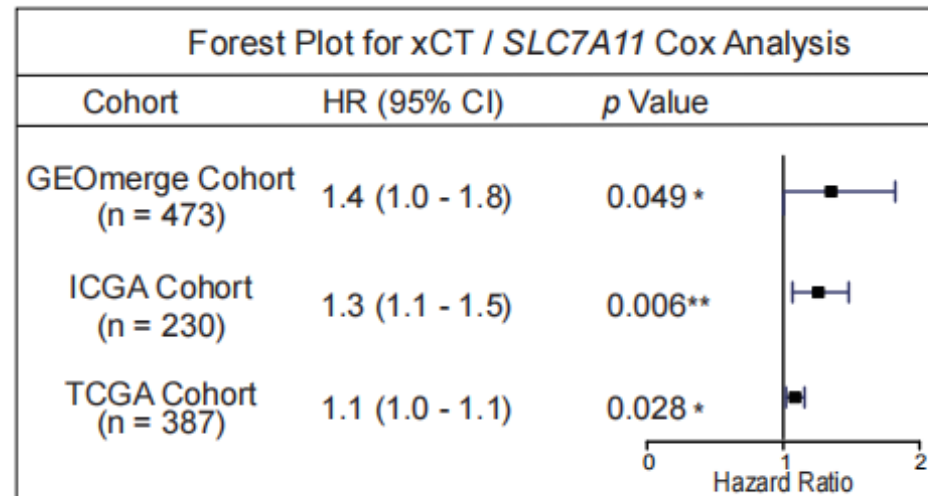
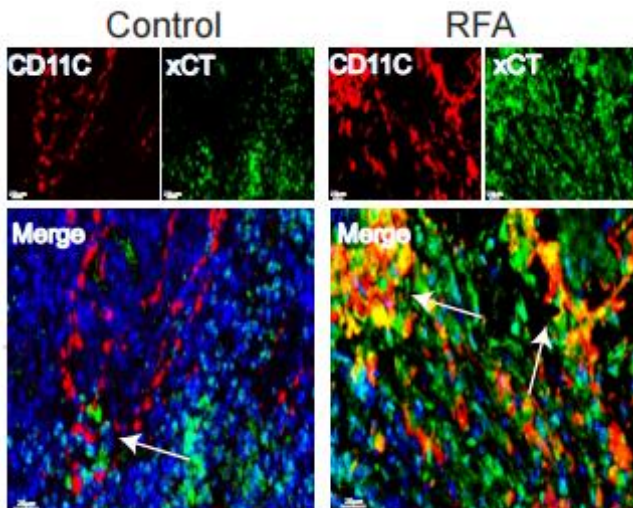
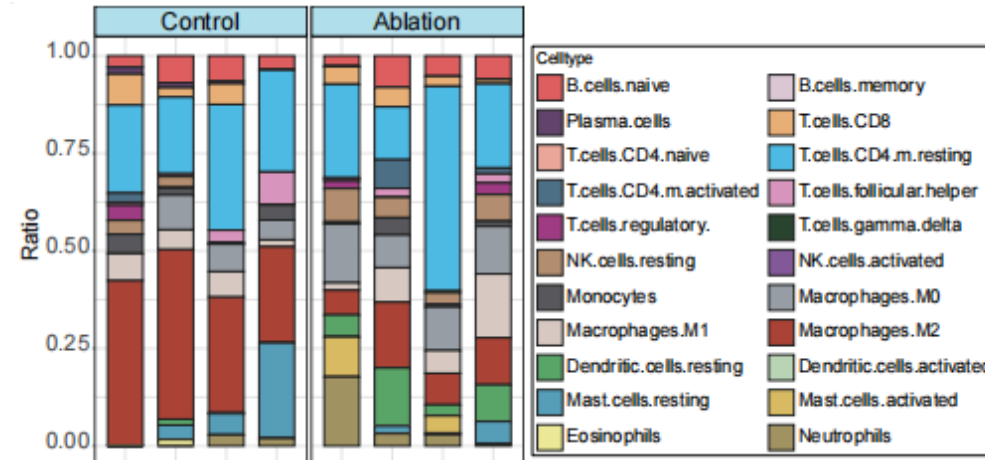
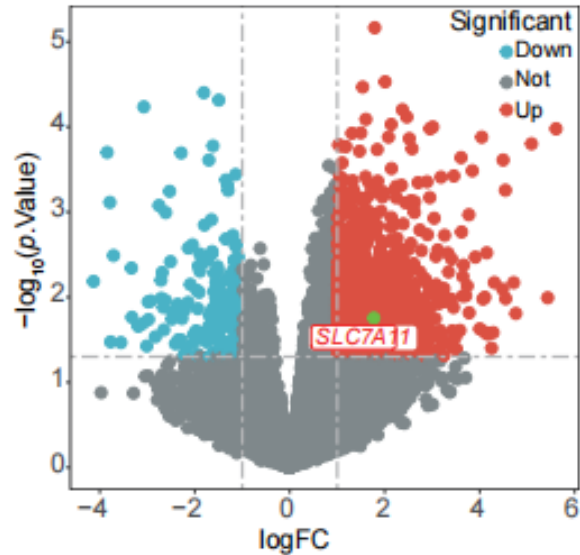
Graphical Abstract



- After RFA treatment in patients with liver cancer, the expression of *SLC7A11* / xCT and the proportion of DCs in the TME were significantly increased.
- *SLC7A11* / xCT is a poor prognostic marker for liver cancer and is mainly expressed in DCs in the TME.
- Targeting xCT in DCs combined with RFA significantly enhances anti-tumor immunity, suppressing tumor growth and offering a promising strategy for improved therapeutic outcomes in liver cancer.

Results

◆ Upregulation of SLC7A11 / xCT Post-Ablation in DCs

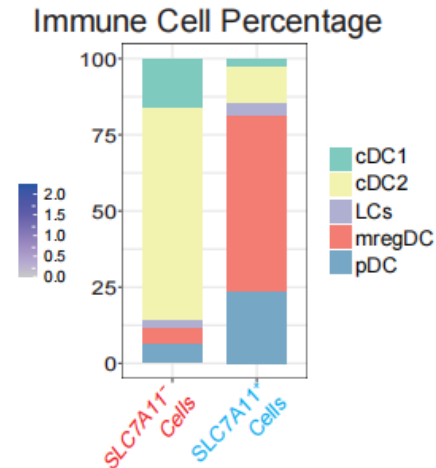
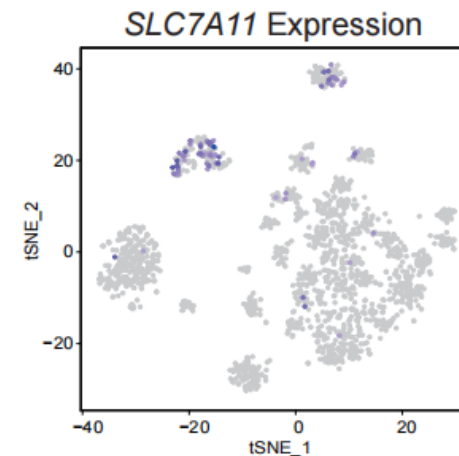
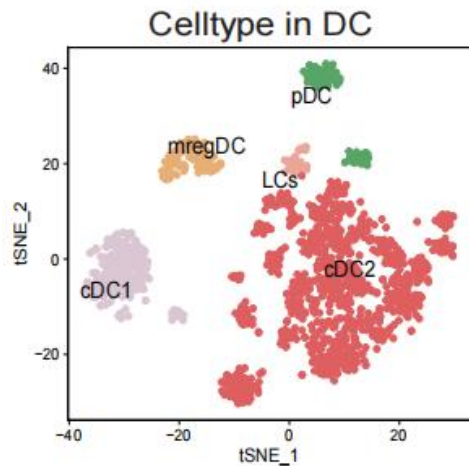
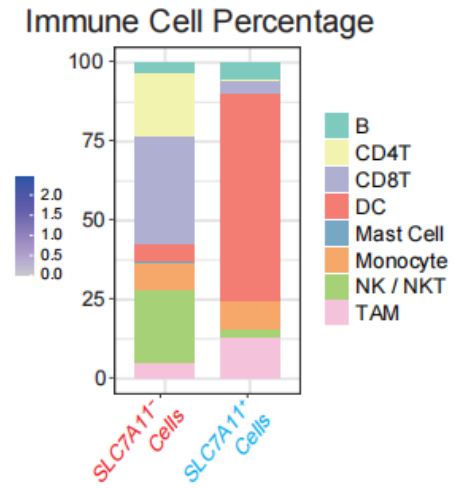
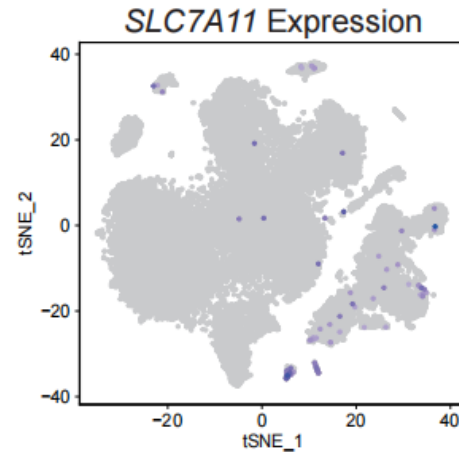
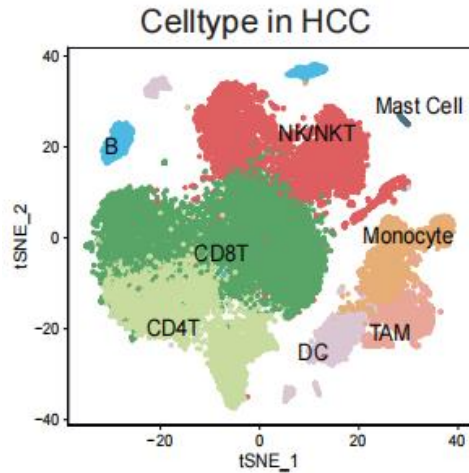


We initially explored *SLC7A11* expression in immune cells at the single-cell level and showed that the highest proportion of DC in the *SLC7A11* + cell composition, suggesting that *SLC7A11* may function in the TME mainly through DC.

Through standardized analysis process clustering and subgroup marker gene alignment, we identified five DC subgroups, namely cDC1, cDC2, pDC, LCs and mregDC. We found that *SLC7A11* is highly expressed primarily in mregDC.

Results

◆ *SLC7A11* is highly expressed in DCs.

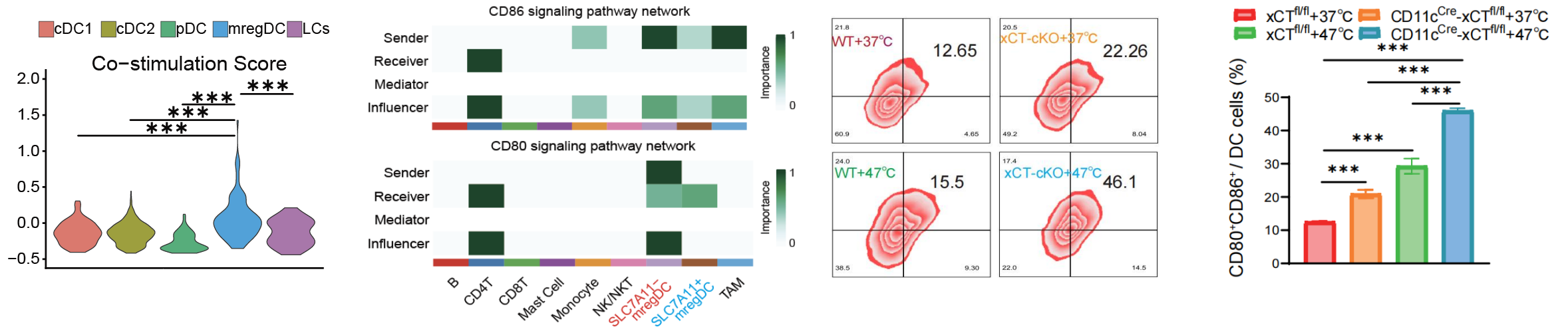


We observed the expression of *SLC7A11* in the immune cell population and found that the the *SLC7A11*⁺ cell composition expression was high, but the proportion of DCs in was close to 70%, suggesting that *SLC7A11* may mainly play its role in TME through DCs.

Through standardized analysis process clustering and subgroup marker gene alignment, we identified five DC subgroups, namely cDC1, cDC2, pDC, LCs and mregDC. We found that *SLC7A11* is highly expressed primarily in mregDC.

Results

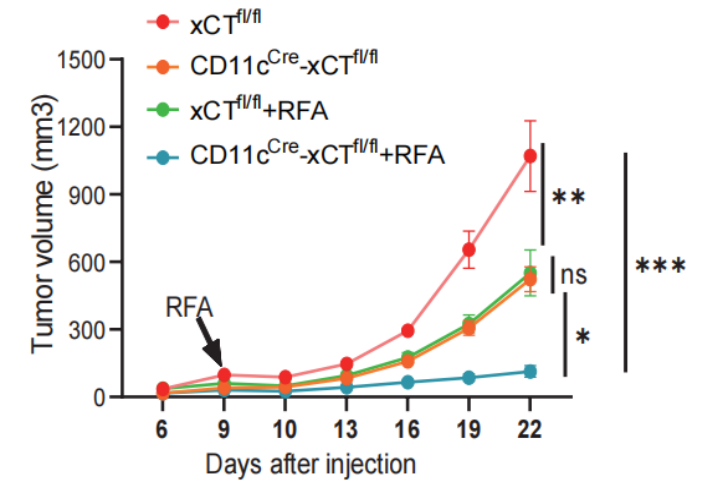
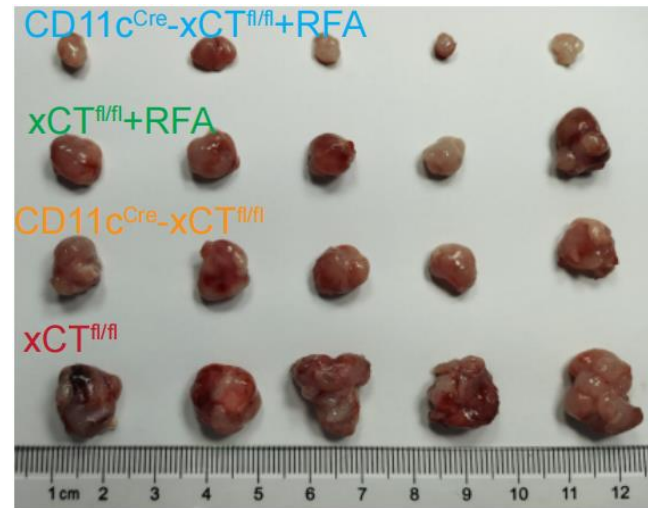
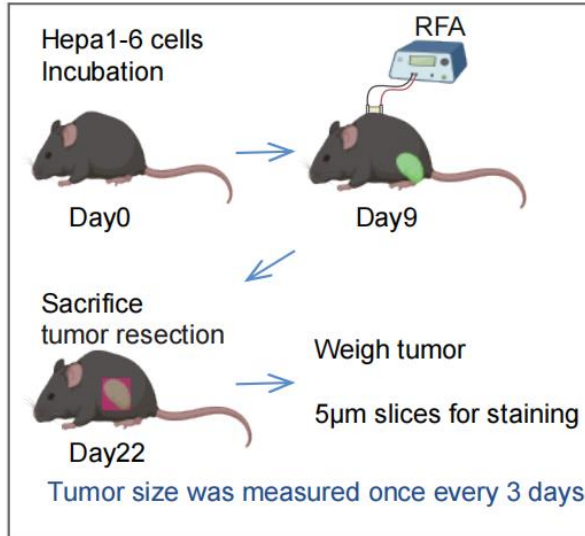
◆ *SLC7A11* Inhibit the costimulatory ability of mregDC



Cell communication and module scoring indicate that mregDC has strong costimulatory ability, and the expression of *SLC7A11* in mregDC cells significantly inhibited the expression of costimulatory molecules such as CD80 / CD86. To verify the role of xCT in DC, we constructed xCT^{fl/fl} mice and CD11c^{cre}-xCT^{fl/fl} mice and performed in vivo experiments. We simulated in vivo RF ablation with in vitro heat treatment and showed that the heat treatment significantly increased CD80 / CD86 expression of BMDC in xCT^{fl/fl} mice, an effect that was more pronounced in CD11c^{cre}-xCT^{fl/fl} mice.

Results

- ◆ RFA was combined to targets *SLC7A11* / xCT in DC to inhibit tumor growth



Hepa1-6 cells were seeded subcutaneously into xCT^{fl/fl} and CD11c^{cre}-xCT^{fl/fl} mice, and local tumors were treated with RFA on day 9, killed and dissected on day 22. Tumor volumes were measured every three days, and the stripped tumor growth curves were plotted. The results showed that tumor regression was more pronounced in CD11c^{cre}-xCT^{fl/fl} mice than in xCT^{fl/fl} mice after RFA treatment.

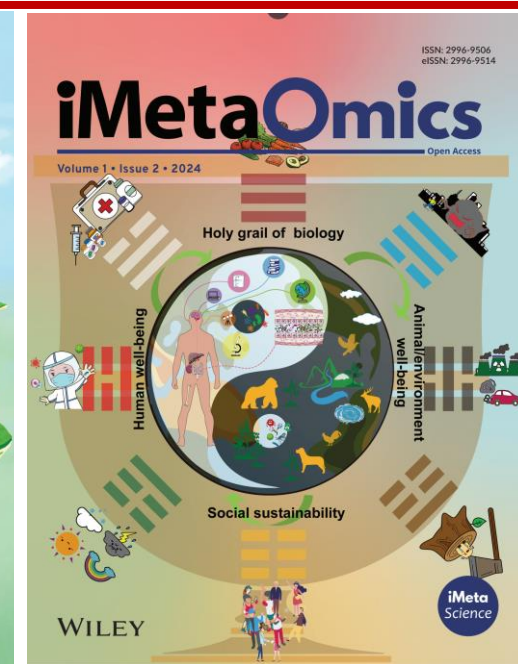
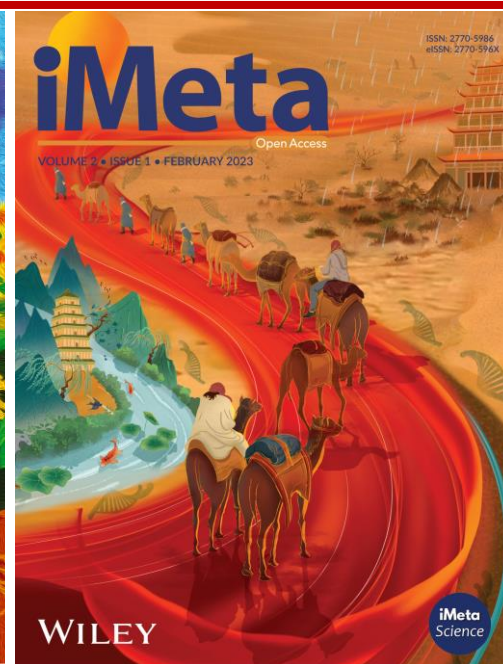


Summary

- ❑ This study revealed that the ratio of DCs to SLC7A11 was upregulated after RFA and that SLC7A11 was mainly expressed in DCs in the microenvironment.
- ❑ This study has demonstrated that SLC7A11 plays an immunosuppressive role in dendritic cells and may be one of the factors for poor prognosis in HCC.
- ❑ This study explored the feasibility of targeting SLC7A11 within DC in combination with RFA, provide new insights into the treatment mode of HCC.

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