Introduction: ICI for Cancer Treatment

Immunotherapies have revolutionized the landscape of clinical oncology, being established as first-line treatments in multiple advanced cancer types, including melanoma, non-small cell lung cancer (NSCLC) and renal cell carcinoma. Despite the strong efficacy of immune checkpoint immunotherapy (ICI), less than 20% of patients show complete or durable response. While studies have shown that infiltration of immune cells in the tumors and high tumor mutational burden (TMB) are key correlates of response to ICI, accurate prediction of patient responsiveness to ICI remains an important challenge. Greater predictivity certainly would increase patient survival and quality of life, by reducing the number, duration, and side-effects of treatments as well as associated economic burden.

Membrane-bound OVA makes tumors more immunogenic:
- Tumor progression slows with membrane-bound antigen expression due as increased intra-tumoral immune response with increased CD8+ and NK cell infiltrates as well as prolonged survival

Membrane-bound OVA increases systemic antigen-specific immune response:
- Membrane-bound antigens trigger systemic T cells and humoral immune responses in tumor-bearing mice

Response to anti-PD1 Treatment:
- Tumors with high dose of membrane-bound antigen are completely responsive to anti-PD1 immunotherapy
- Tumor rejection upon anti-PD1 treatment mostly relies on the effects of CD8+ T cells, but requires the activities of CD4+ T cells for full efficacy. Surprisingly, tumor rejection was not depending on the presence of mature B cells and antibody
- Mice that underwent complete remission of B16mOVA upon anti-PD1 treatment can significantly delay the growth of B16 WT tumors, suggesting antigen spreading immune mechanism

Materials and Methods

1. Design and Characterization of the engineered B16 Melanoma Cell Lines:
- B16-F10 melanoma cells were modified to express membrane-bound or soluble full-length ovalbumin (B16ova and B16sOVA, respectively), at high [+] or low [-] levels
- Figure 1. Characterization of OVA-expressing B16-F10 melanoma cell lines
- Figure 2. OVA surface characterization
- Figure 3. Effects of membrane-bound antigens on melanoma tumor immune response
- A. Tumor growth of the different OVA-expressing lines in vivo (B16ova and B16sOVA, respectively), at high (+) or low (-) levels
- B. Flow cytometry
- C. Tumor volume of B16ova or WT mice treated with immunotherapy
- D. In vivo tumor cell population infiltrated in the different tumors as day 10 post-injection analyzed by flow cytometry

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Conclusions

Membrane-bound antigens enhance tumor immunogenicity and responsiveness to ICI in melanoma mice model
- We anticipate that our results could be applied to humans and improve cancer patient response to ICI predictability with potential implications in establishing future clinical guidelines to direct the choice of treatment toward ICI

Impact: Implementation in the Clinic

- Apply to 3 independent human datasets with 1722 patients treated with ICFA
- The proportion of membrane neoantigens correlates with increased survival in cancer patients treated with ICI therapies
- Could be use in combination with TMB to improve immunotherapy treatment