Patient-derived MicroOrganoSpheres (MOS)™ and clinical response to immunotherapy

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Background

Immunotherapies, including immune checkpoint inhibitors (ICI), have revolutionized the treatment of many cancers, producing significant improvements in survival. However, the intended anti-tumor effects also result in a unique form of autoimmunity, known as immune-related adverse events (irAEs), which have emerged as a limiting factor for immunotherapies. Cutaneous irAEs (cirAEs), the most frequently occurring ICI–related toxicities, have been associated with improved efficacy and survival but, in their severe forms, require systemic steroids and have in some cases led to premature ICI discontinuation and even fatality. Thus, there is a clear need for both robust biomarkers as well as adequate models that effectively predict patient outcome.

Methods

Using-microfluidic droplet technology that generates "mini" patient-derived organoids called MicroOrganoSpheres (MOS), we successfully generated skin MOS from skin biopsy samples in both healthy and tumor derived skin that sustained the original patient skin immune microenvironment over three weeks. Using this model, we characterized these MOS and assessed skin cell toxicity to ICI and targeted therapies.

Results

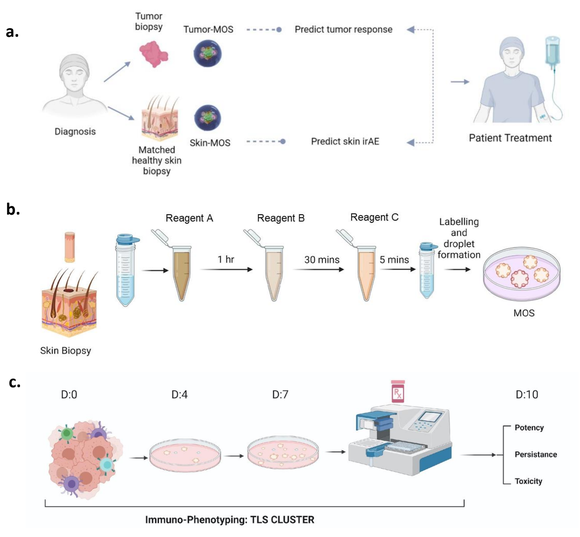

Figure 1. ***Schematic representations*** of (a) an immune-competent MOS model to predict ICI treatment outcome, (b,c) the workflow used to establish MOS from skin samples

Results

CHARACTERIZATION OF SKIN MOS

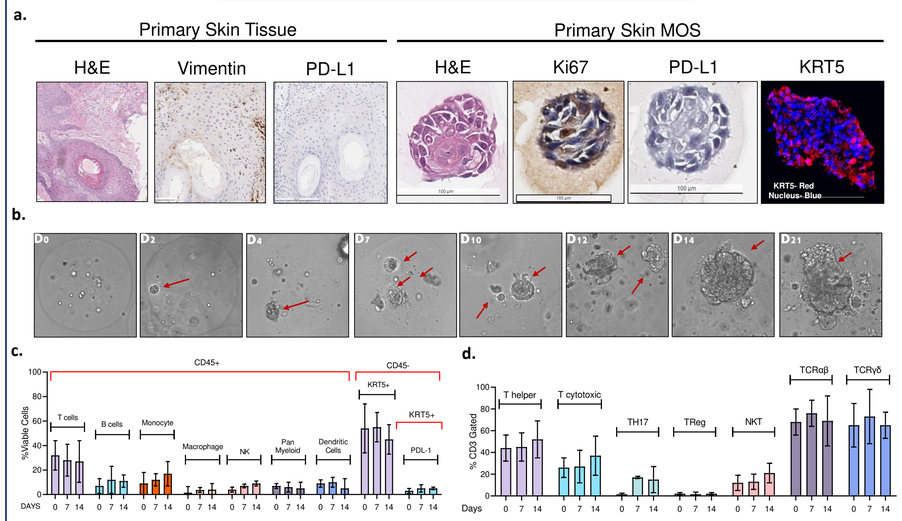

Figure 2. ***Skin MOS were successfully generated from autopsy and freshly surgically resected skin tissue***. (a) Representative images of primary normal skin tissue, characterized by H&E, Vimentin high, and PD-L1 low, retaining a skin specific marker (KRT5) and continuing to replicate (Ki67+). (b) Representative images of skin MOS establishment on days 0, 2, 4, 7, 10, 12, 14, and 21. (c) Time-series flow cytometry analysis reveals that the relative abundance of skin and immune cell subtypes, as well as (d) MOS infiltrating CD3+ T cell subsets, were maintained in the MOS culture over a period of 14 days.

CHARACTERIZATION OF MATCHED PATIENT BIOPSIES

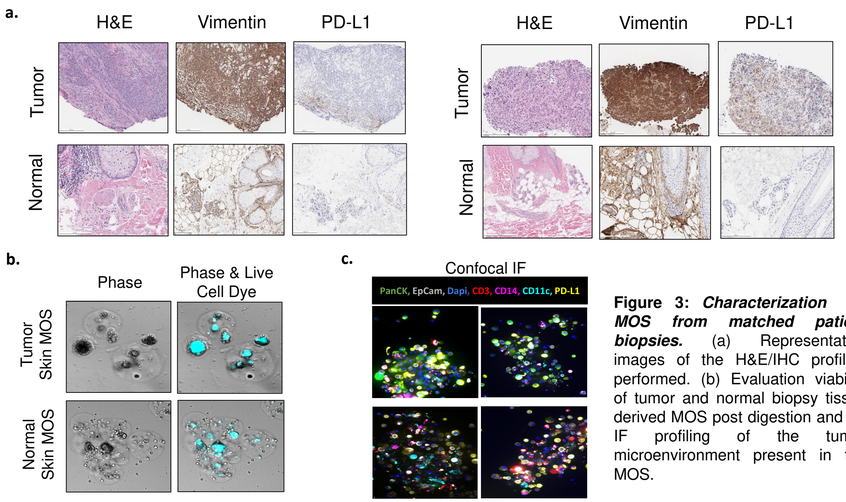

Figure 3: ***Characterization of MOS from matched patient biopsies.*** (a) Representative images of the H&E/IHC profiling performed. (b) Evaluation viability of tumor and normal biopsy tissue derived MOS post digestion and (c) IF profiling of the tumor microenvironment present in the MOS.

Results

SKIN MOS CLINICAL RESPONSE TO IMMUNOTHERAPY

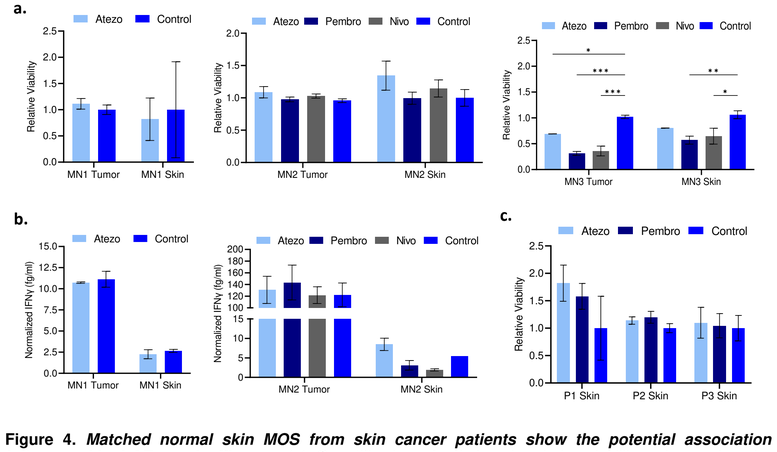

Figure 4. ***Matched normal skin MOS from skin cancer patients show the potential association between skin irAEs and efficacy.*** (a) Quantification of relative drug-induced killing observed under indicated treatment for 6 days in MOS generated from melanoma tumor tissue and matched skin biopsies from three melanoma patients (MN1, MN2, MN3). (b) Expression of IFNγ post the indicated treatments for 6 days. (c) Quantification of relative drug-induced killing observed under indicated treatment for 6 days in MOS generated from normal skin tissue biopsies from three metastatic skin caner patients (P1, P2, P3; tumor tissue was not collected).

Conclusion and Future Directions

This study demonstrates the potential application of a patient-derived, immune competent, skin model for assessing ICI efficacy and toxicity response. Response of matched tumor and skin MOS from the same patient to ICI treatments was measured, which may provide an assay for assessing ICI efficacy and irAE in the clinic. Further clinical study to demonstrate the application of this model to predict outcomes is necessary.

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