The types of response to anti-PD-1 therapy are not well understood.

Published models often predict treatment responses including complete response, non response, and stable response only at a fixed time point.

Our goal was to elucidate the mechanisms driving tumor stability under immunotherapy, and to identify key factors affecting tumor response to treatment.

We expanded a previously qualified mechanistic immuno-oncology (I-O) QSP model representing a late-stage solid tumor to explore tumor cell heterogeneity, necrotic core dynamics, and mediator regulation.

The model includes a representation of tumor and immune cell life cycles and their interactions (Figure 1) focusing on the tumor cell growth and response.

**Introduction**

**Objectives**

- A local sensitivity analysis identified key parameters determining response to anti-PD-1 therapy including MHC and PD-L1 expression (Figure 2)
- Sensitive parameters were sampled using a distribution centered at a physiological value where each sampled value is simulated to assess change in tumor volume.
- Simulations with unphysiological behavior in both the untreated and treated scenarios were excluded.
- Analysis of batch simulations (n = 40,000) was performed using a K-means clustering algorithm in MATLAB® to identify representative responses to anti-PD-1 therapy.

**Results**

**Heterogeneous tumor cell populations are sufficient to reproduce all types of tumor response**

Baseline MHC expression rate parameters were varied from 0% to 100%. Baseline PD-L1 expression levels were varied over a range between 10% to 100% of baseline value. Over 40,000 variants were simulated and distinct clusters are highlighted (red lines).

- Varying the MHC expression of a homogeneous tumor cell population was sufficient to reproduce tumor escape, linear growth, tumor rebound, delayed response, and stable response following initial reduction or growth.
- Varying the PD-L1 expression of a homogeneous tumor cell population has limited variability in the types of response.
- Only defined levels of MHC or PD-L1 expression result in a stable tumor volume that persists for more than 100 days.

**Varying the magnitude of cytokine regulation was not sufficient to reproduce most types of tumor response**

The model includes a representation of tumor and immune cell life cycles and their interactions.

**A necrotic core explains the resistance to tumor regression in certain scenarios**

- Tumor cells with identical MHC and PD-L1 expression experienced a faster and greater volume reduction without a necrotic core (Figure 4, right panel).
- A tumor without a necrotic core is likely to regress sooner because the clearance of necrosed cells is generally slower compared to typical tumor cell clearance.
- A necrotic core may remain in the tumor following a reduction in the number of activated antigen-presenting cells due to diminishing tumor antigen levels.
- Even without a necrotic core, a tumor may persist because the MHC negative cells can evade cytotoxicity.

**Conclusions**

- Mechanistic modeling identified critical factors that may explain the diverse types of tumor response to anti-PD-1 therapy including stable response.
- The critical determinant for stable response was a pool of MHC negative tumor cells which evade cytotoxicity and maintain the tumor volume.
- The necrotic core has greater impact in the initial stages of tumor response compared to later time points.
- Cytokine regulation of cellular clearances may be relatively insignificant for tumor response to anti-PD-1.
- Further research into the effects of tumor cell mutation in MHC, PD-L1, and other mechanisms may elucidate other factors that contribute to variability in clinical responses.