Development of a mechanistic representation of a stable solid tumor

Douglas Chung, Michael Weis, Christina Friedrich, Vincent Hurez, Rebecca Baillie, Katherine Kudrycki

Rosa & Co., San Carlos, CA

Introduction

- The mechanisms determining stable response of a solid tumor to anti-PD-1 therapy are not well understood
- Published models[1] often predict treatment responses including complete response, non response, and stable response only at a fixed time point

Objectives

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

Methods

- We expanded a previously qualified[2] mechanistic immuno-oncology (I-O) QSP model[3] 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[4,5] (Figure 1) focusing on the tumor cell growth and response

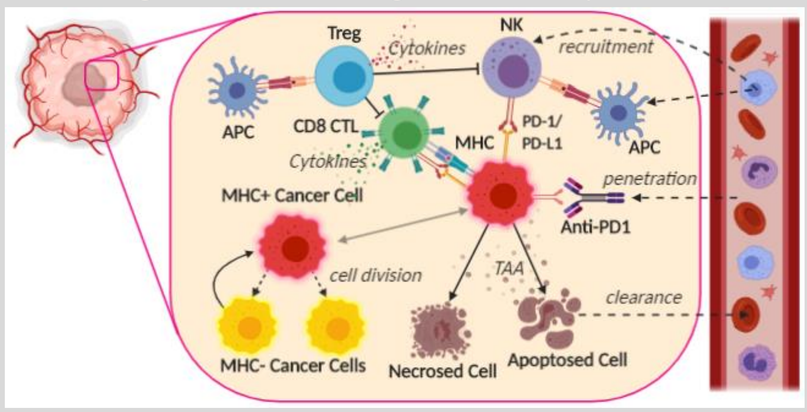

Figure 1. Overview of biological components and functions in the I-O QSP model.

- 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[6]
- 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

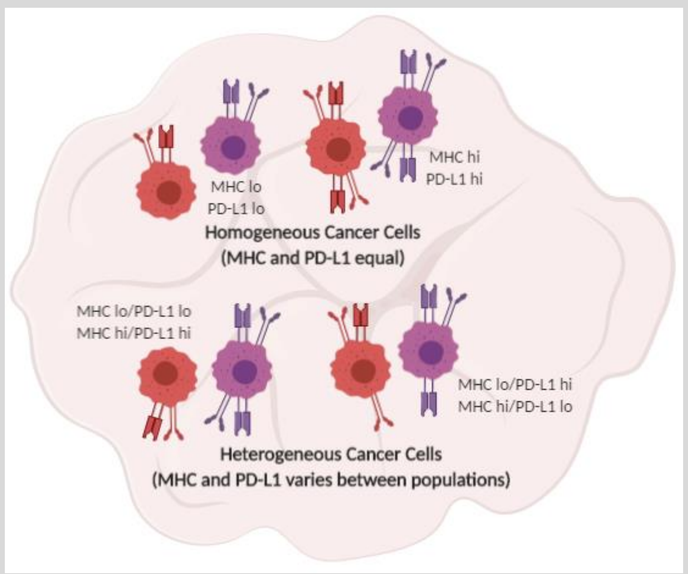

Figure 2. Overview of types of cancer cell populations used in the model.

References

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Results

Variability in MHC or PD-L1 expression is sufficient to reproduce most types of tumor response

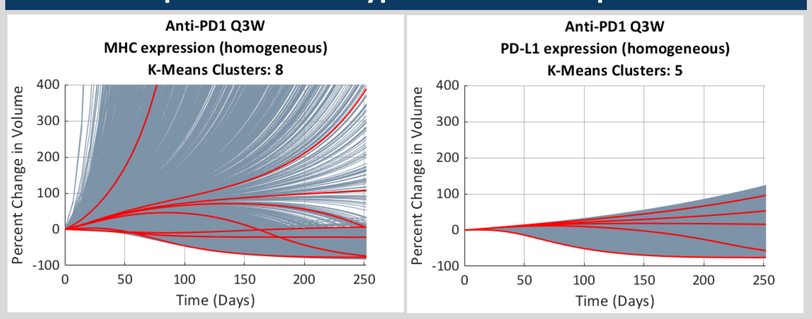

Figure 3. The impact of MHC and PD-L1 expression levels were explored using homogeneous cancer cell populations. Baseline MHC expression rate were varied from -95% to +3000%. Baseline PD-L1 expression levels were varied over a range between 10^{-2} to 10^{4} of baseline value. Over 40,000 variants were 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 homogenous 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

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

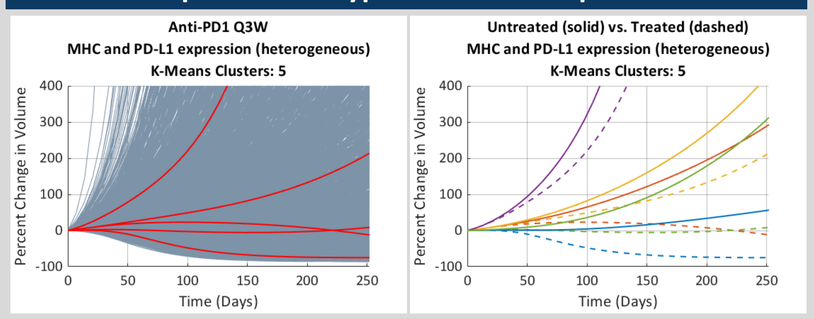

Figure 4. MHC and PD-L1 expression levels were varied simultaneously using two distinct tumor cell populations. Baseline MHC expression rate parameters were varied from -95% to +3000%. Baseline PD-L1 expression levels were varied over a range between 10^{-2} to 10^{4} of baseline value. Over 40,000 variants were simulated and distinct clusters are highlighted (red lines).

- Independently varying the MHC and PD-L1 expression creates all possible types of tumor response (Table 1)
- Tumors with similar untreated growth trajectories may respond differently to anti-PD1 therapy solely due to differences in MHC and PD-L1 expression

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

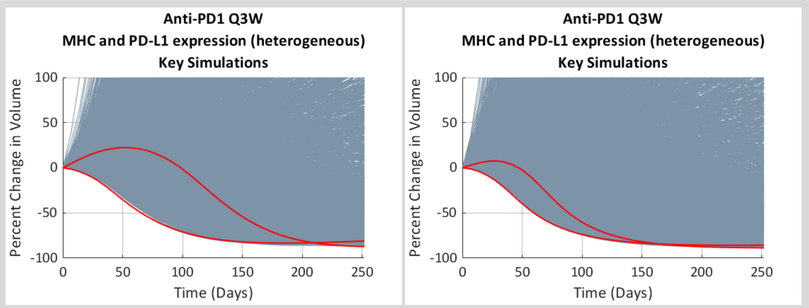

Figure 5. Heterogenous tumor cell populations with varying expression levels of MHC and PD-L1 were simulated with (left) and without (right) a necrotic core.

- 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

Results

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

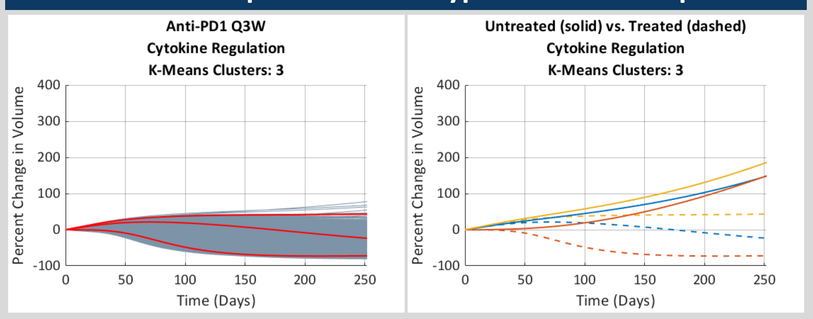

Figure 6. A qualified virtual solid tumor was used to explore the impact of cytokine regulation on tumor response to anti-PD-1 therapy. The maximum effect of cytokines on APC, NK, CD8+ CTL, CD4+ T helper, CD4+ Treg cells were varied 0% to 100%. 10,000 tumor variants were simulated and distinct tumor response-types were identified using a K-means clustering algorithm.

- While cytokines are important in regulating immune cells and cytotoxicity, the impact of this regulation on clinical outcomes, such as tumor volume, is not well understood
- Although cytokine effects on the clearance of immune cells have been reported[8], simulations show a minimal impact on tumor response to anti-PD-1 therapy

A range of responses to anti-PD-1 can be simulated by exploring variability in MHC and PD-L1 expression

- The types of response to anti-PD-1 treatment is similar for both homogeneous and heterogeneous tumor cell populations when varying only MHC expression or only PD-L1 expression (Table 1)
- Having heterogeneous cell populations with varying levels of MHC and PD-L1 expression produces all types of responses including a new response type, delayed escape

Response to anti-PD1 therapy	Complete/ Partial Response†	Delayed Response	Stable Volume	Delayed Escape	Tumor Rebound	Progressive Disease†
No MHC mechanism	X (complete)	X				X
Homogeneous/ Heterogeneous MHC	X* (partial)	X	X		X	X
Homogeneous/ Heterogeneous PD-L1	X* (partial)	X	X			X
Heterogeneous PD-L1 and MHC	X* (partial)	X	X	X	X	X
Complex Mediator Regulation	X* (partial)	X	X			

Table 1: Summary of the diverse tumor response-types to anti-PD-1 therapy achieved by evaluating different hypotheses. Delayed response means initial tumor growth followed by tumor regression after 36 weeks. Stable volume means constant tumor volume is for over 100 days (< ±5% change). Delayed escape means minimal tumor volume change (±10%) followed by progression. Tumor rebound means initial regression followed by progression.
*: Partial response due to remaining necrotic core; †: RECIST criteria[7]

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

For more information about this work, please contact:
Douglas Chung, MS, dchung@rosaandco.com