Stochastic Modeling Quantifies Tumor Elimination and Evasion in the Setting of Immunotherapy

Jason T. George[1,2] and Herbert Levine[1,3]

***Short Abstract* — We propose a mathematical model between tumor and CD8+ T-cell adaptive immune compartments. This framework accurately models relevant empirical features, including the growth-threshold conjecture of immune activation, and predicts experimental observations including 'sneak-through,' wherein intermediate growth threats are penalized relative to their slower and faster counterparts. We find agreement between our model and AML age-dependent incidence as a function of decreasing immune turnover and repertoire size. Lastly, we quantify therapeutic efficacy of neoadjuvant immunotherapeutic strategies in the setting of an immune evading threat. Our model serves as a first attempt at modeling stochastic cancer evolution alongside an adaptive immune compartment.**

***Keywords* — Cancer immunotherapy, applied probability, acquired immune evasion.**

I. Introduction

THE adaptive immune system plays an integral role in immuno-editing, and cancer progression occurs only if a tumor successfully evades immune detection [1]. Immunotherapy is responsible for recent breakthroughs in cancer treatment and encompasses strategies aimed at enhancing the patient's immune system via a number of mechanisms, including tumor antigen vaccines [2], immune checkpoint inhibition [3], and Chimeric Antigen Receptor T-cell (CAR-T) therapy [4].

Despite this improvement, durable clinical outcomes are still limited as tumors are capable of acquiring treatment-resistant clones during disease progression [5], and cancer cells exploit a variety of strategies to avoid CD8+ T-cell elimination [6], including downregulation MHC-I [7], preventing CD8+ recognition altogether. Prior studies have considered systems level interactions between the tumor and host adaptive immune system [8,9]. An independent research effort has investigated acquired drug-resistance during clonal evolution [5,10]. At present, the time-dynamic effect of acquired immune evasion on tumor development under adaptive immune surveillance remains uncharacterized. Understanding the successes, and failures, of adaptive immune system co-evolution with tumor cells from a population dynamical level would enhance our understanding of immunotherapy, enabling quantitative predictions of treatment success.

Here, we describe a foundational model between cancer and the adaptive immune system wherein tumor cells may be recognized by the immune cells but may also acquire an immune-evasive phenotype. We show that our model predicts empirically observed 'sneak-through' in that threats with large and small net growth rates have a preferential advantage over those with intermediate growth rates [11]. We characterize AML incidence as a function of immune turnover and repertoire diversity and conclude by quantifying the benefit of immunotherapy and predicting treatment-specific advantages based on tumor growth rates and immune competency.

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[1]Center for Theoretical Biological Physics and Department of Bioengineering, Rice University, Houston, TX, USA.

[2]Medical Scientist Training Program, Baylor College of Medicine, Houston, TX, USA. E-mail: jason.george@rice.edu

[3]Department of Physics and Astronomy, Rice University, Houston, TX, USA. E-mail: herbert.levine@rice.edu

II. Results

A. Cancer sneak-through predicted via increased immune evasion

Preferential immune escape and immune evasion are predicted for threats with small and large growth rates over those of intermediate growth rates.

B. Age-specific AML incidence characterized by diminishing adaptive immune system

AML incidence data is quantified by an immune system that diminishes in age and is therefore at increased risk of tumor escape and evasion.

C. Enhanced survival predicted for immunotherapy

We end by estimating treatment success probabilities for CAR-T and tumor vaccine immunotherapies.

III. Conclusion

Our model is consistent with empirical observations, predicts the likelihood of cancer progression due to immune escape and evasion, and may be used in the future to quantify immunotherapy's enhanced tumor control.

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