Title: Systems biology approach to understanding the immune system of prostate cancer post-castration

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Background: The prostate cancer (PCa) is the most commonly diagnosed malignancy and the second leading cause of cancer-related deaths in American men. Androgen ablation (chemical castration or surgical castration) is a first-line therapy for PCa, but a significant number of patients eventually developed castration-resistant PCa, for which there is no cure. Thus, understanding the long-term impact of androgen ablation on the host immune system will play critical roles in the development of effective immune therapies for advanced PCa. Methods: In prostate-specific Pten-/- mice model, our lab has previously shown that CD8+ effector function is transiently increased following surgical castration (CX). To determine the inhibitory mechanisms responsible for the transient increase in effector function, a unique multipronged systems biology approach has been proposed in this study, which combines coherent experimental protocols with a predictive multi-scale (molecular level, cellular level, and tumor tissue level) multi-compartment (prostate compartment, blood vessel compartment, prostate draining lymph node compartment, and spleen compartment) ODEs model of immune system (called M5I system) to dissect the complicated dynamics of the immune responses to castration in prostate cancer mice model. The proposed M5I system integrated four types of datasets (i.e., Flow cytometry, IHC, RT-PCR, and RNA-Seq) under three types of experimental conditions (i.e., before/after CX or perturbations) involving tumor, androgen, cytokines/chemokines and related pathways, and immune cells in different compartments in the whole immune system, and was trained by a proposed algorithm called modified genetic algorithm (MGA), a novel implementation of traditional GA by taking advantage of HPC in TACC.

Results: A potential mechanism responsible for the transient increase in effector function was resulted from the proposed systems biology approach, demonstrating that two feedback loops, one negative feedback loop between CTL and Treg bridged by IL-2, and the other positive feedback loop between Treg and CCL20 bridged by TAN, amplify the inhibitory immune function, which further inhibits the effector immune function, meanwhile the specific signaling pathways related with the secretion of IL-2 from CTL and the secretion of CCL20 from TAN and the absorption of IL-2 and CCL20 by Treg were also identified from TAN-Seq data. Three potential intervention targets were further identified (mathematically predicted and experimentally validated) from the proposed approach, including TAN, CCL20, and systemic Treg, whose individual depletions all can improve the outcomes of castration therapy. In addition, extended therapeutic protocols targeting the identified variables in the system were mutually compared in silico and different patterns of treatment effects were suggested for the design of optimal therapeutic strategy. Finally, long-term effects of the selected treatments were also discussed.

Conclusion: This study provides a framework of systems biology approach to studying tumor-related immune mechanisms and consequent therapeutic strategy selection in order to improve outcomes following immunotherapy.