Systematically understanding the immunity leading to CRPC progression

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Introduction

■ Prostate cancer (PCa) is the most commonly diagnosed malignancy and the second leading cause of cancer-related deaths in American men.

■Androgen deprivation therapy (ADT) has become standard treatment modalities of PCa. However, most of PCa will eventually become unresponsive and recur within 1-3 yeas after ADT as castration-resistant prostate cancers (CRPC).

■ Previous studies have demonstrated that androgen receptor (AR) signaling pathway play a central role in CRPC and constitutes an attractive target for therapy. However, the treatment of PCa with AR antagonists can also acquire resistance through AR mutations.

■ Recent studies indicate that the tumor-associated macrophages (TAM) exerts a negative impact on the treatment response of PCa after ADT.

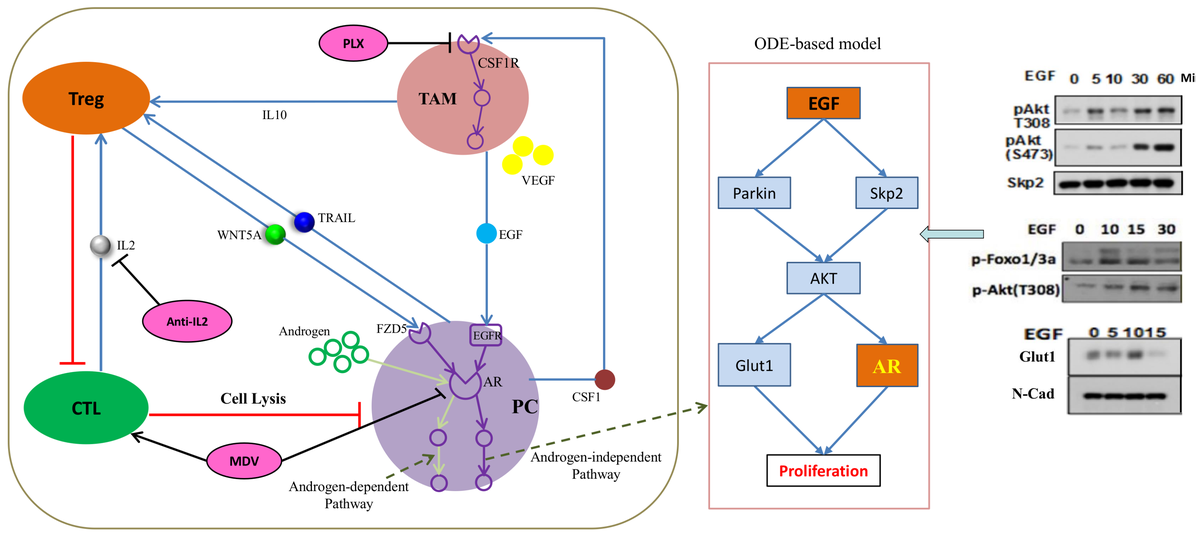
■ Our experiments show that the frequency of CD8+ T cells (CTLs) were increased at the early stage but reduced later following ADT. The secreted IL2 by CTLs promoted Treg expansion, which in turn suppressed CTL proliferation. Also, WNT5A secreted by Treg activated AKT/AR pathways and stimulated PCa cell proliferation.

■ Above observations indicate that the immunosuppressive microenvironment (mE) in PCa appears be responsible for the failures of various immunotherapies.

■ We proposed a predictive 3D hybrid multi-scale model (HMSM) for systematically understanding the immunity leading to CRPC progression.

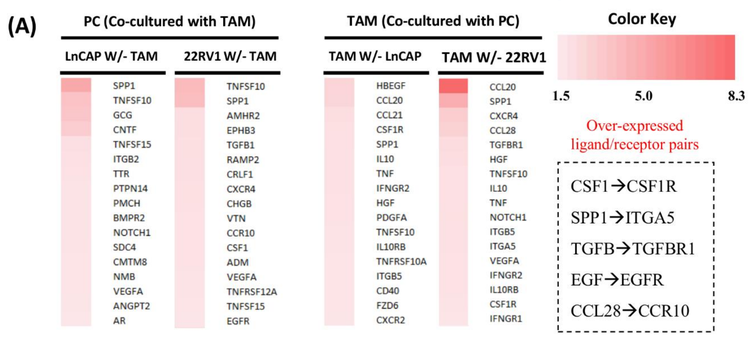
Systems Modeling Strategies

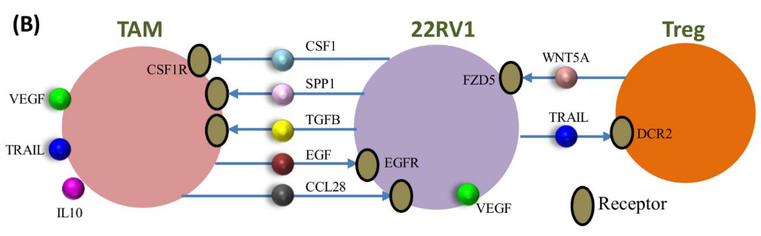
The 3D hybrid multi-scale Agent-based Model of CRPC (HMSM)



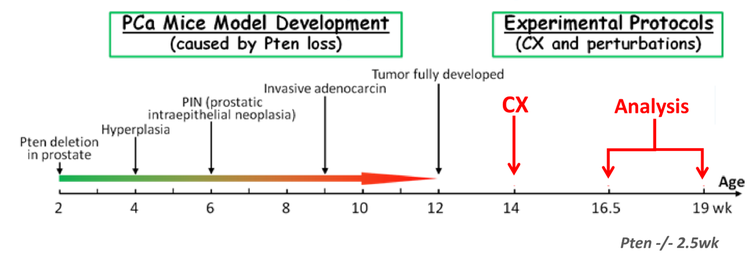
Data Generation and Analysis

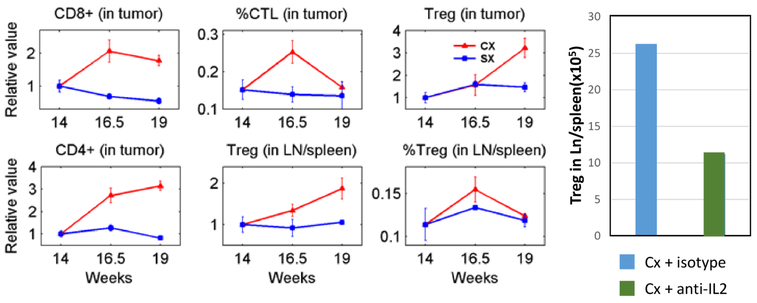
Cell-cell interactions inferred from RNA-seq data



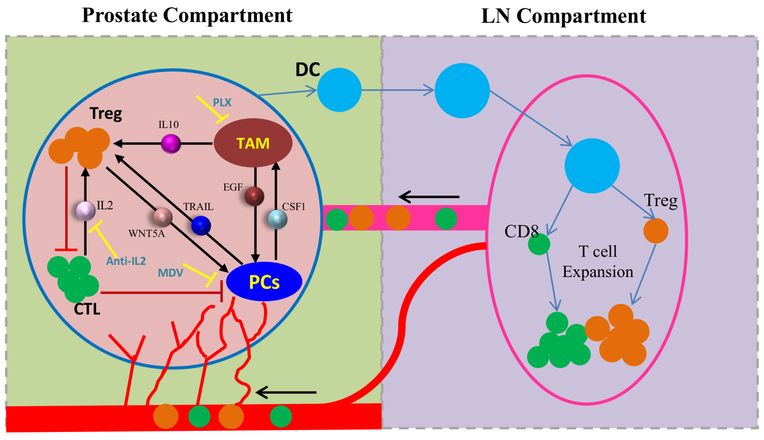


Animal model development and data generation





System modeling diagram



Modeling Intracellular Signaling Pathways of PC with ODEs

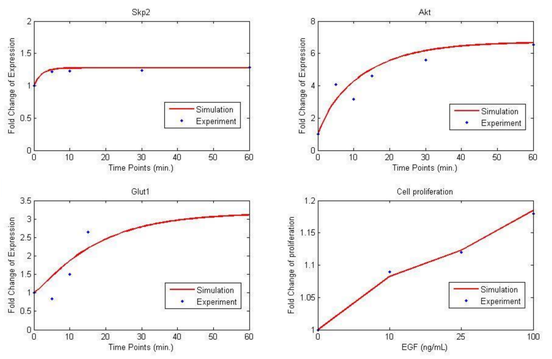
$$\frac{d[Parkin]}{dt} = k_1 \frac{[EGF]}{H_1 + [EGF]} - d_1[Parkin]$$

$$\frac{d[Skp2]}{dt} = k_2 \frac{[EGF]}{H_2 + [EGF]} - d_2[Skp2]$$

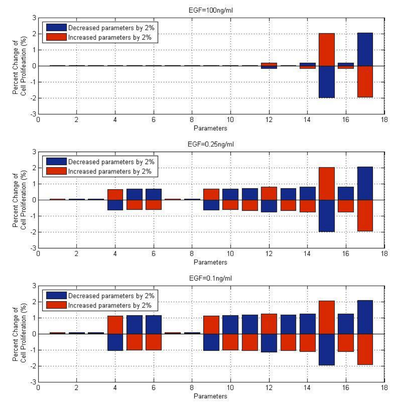
$$\frac{d[AKT]}{dt} = k_3 \frac{[Parkin]}{H_3 + [Parkin]} + k_4 \frac{[Skp2]}{H_4 + [Skp2]} - d_3[AKT]$$

$$\frac{d[Gly]}{dt} = k_5 \frac{[AKT]}{H_5 + [AKT]} - d_4[Gly]$$

$$\frac{d[prol]}{dt} = k_6 \frac{[Gly]}{H_6 + [Gly]} - d_5[prol]$$



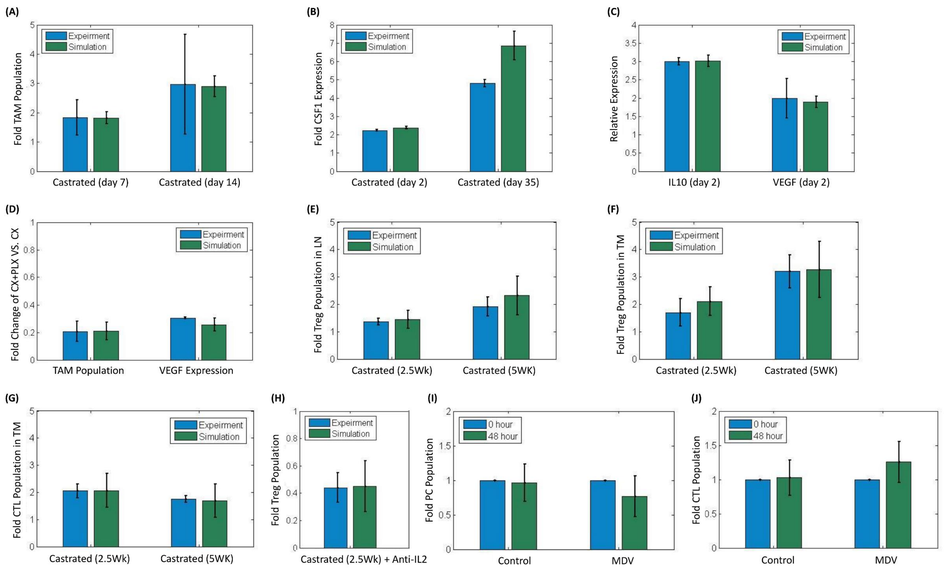
Fitting Curves



Sensitivity Analysis

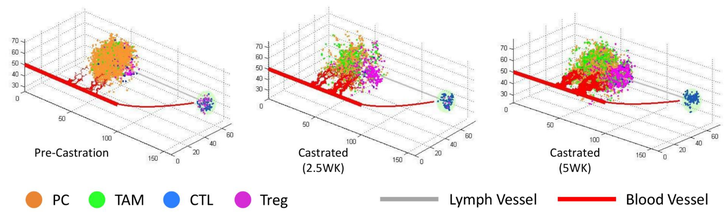
Model Prediction and Biological Validation

Modal Validation under various contexts

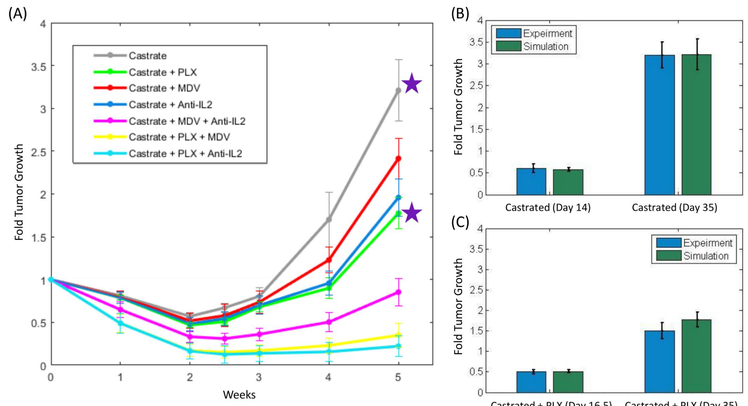


The HMSM model is capable to re-capture the experimental observations from our group and others.

Simulated Tumor Growth



Prediction of combined treatment on CRPC



To identify the potential therapeutic targets for CRPC development in the immune mE, we simulated the effects of single or combined treatments. The predictions of two therapeutic strategies (**purple stars**) were validated by experimental observations.

Conclusions

■ The proposed HMSM model may serve as a novel computational platform for understanding the immunity leading to CRPC progression and provides a potential therapeutic strategy in effectively improving the therapeutic response of ADT for prostate cancer.

■ Our predicted results show that blockade of TAM-PC interaction with PLX and inhibition of Treg proliferation with IL2 antibody have potential to overcome the development of CRPC.

■ In the next step, we will assess two potential treatment strategies with our computational model: PD1 therapy, and Skp2 or parkin targeting.

Acknowledgements

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