Computational Discovery of Novel Immune Checkpoints


1 Computational Discovery of Novel Immune Checkpoints

Introduction

The immune system constantly identifies and destroys malignant cells. Some tumors evade the immune system by expressing co-inhibitory ligands that inhibit T cells. Blocking the co-inhibitory signal allows the T cells to attack the tumor. Checkpoint blockade is a breakthrough approach to cancer therapy with impressive clinical benefits. However, the majority of cancer patients still do not respond and new targets, target combinations and drug modalities are needed.

A. The Concept

Immune genes often have no sequence similarity to any other gene within the organism (have no paralogs). For instance, IL2 and PD-1, do not resemble any other human gene by sequence. If immune related genes, such as cytokines, that have no paralogs by sequence similarity evolved from divergence, there must be a signature in the genome indicative of their related evolutionary origins. We found that gene structure was more conserved than sequence for those genes.

B. Discovery of Novel Immune Checkpoints

Known B7/CD28 proteins have the following typical gene structure:

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  - **ICOS**
  - **BTLA**
  - **PD1**

Based on this gene structure, a BLAST-like algorithm identified BTLA as closest to PD-1 and TIGIT as closest to ICOS. The TIGIT finding was published in 2009 (Proc Natl Acad USA. 2009 Oct 20; 106(42) 7855-7863).

2 Computational Characterization of ImmuneCheckpoint for Cancer Immunotherapy

Normal and Cancer Tissues

Highly enriched in normal immune tissues vs normal solid tissues and expressed in multiple solid tumor types

Immune Cells

PVRIG is expressed and regulated in immune subsets

Tumor Correlation

Most correlated PVRIG genes in cancer are T cell genes

3 Validation of a Novel ImmuneCheckpoint for Cancer Immunotherapy

Identifying PVR2 as the PVRIG Counterpart Suggests PVRIG is in the TIGIT Pathway

Antagonist PVRIG Antibodies Increase CD4+ T cell Proliferation in-vitro

PVRIG Knockout Mice Treated with anti-PD1 Show Tumor Growth Inhibition Compared to Wild Type

PVRIG Blocking Antibody Reduces Tumor Growth in Combination with Anti-PD1 in Mouse Tumor Model

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