Tipping the Balance: The Potential of TIM-3 and LAG-3 Inhibition to Augment Immunotherapy

Andy Ferguson, PhD

March 16, 2016
Overview

• Overview of TIM-3 and LAG-3

• Expression on immune cells in the tumor microenvironment

• Function in limiting anti-tumor immune response

• Expression of TIM-3 and LAG-3 following PD-1 blockade

• Do you always need PD-1 blockade?
Tim-3: A Key Immune Checkpoint and a Next Generation Cancer Immunotherapy Target

- T cell immunoglobulin and mucin domain (TIM) family
- Identified through expression on Th1 cells
- Inhibits T cells in autoimmunity and tumor models
- Potential ligands:
  - galectin-9
  - phosphatidylserine
  - HMGB1
  - CEACAM-1
- Signaling is incompletely characterized (Bat3, Lck)
- Immune cell expression: DCs, T cells, Tregs, NK cells, macrophages, monocytes, MDSCs, mast cells, neutrophils

LAG-3: A Key Immune Checkpoint and a Next Generation Cancer Immunotherapy Target

- Discovered through differential expression on NK cell line activated with IL-2

- Member of Ig superfamily, structurally related to CD4

- Ligand: MHC Class II, galectin-3

- KIEELE domain required for suppressive activity of LAG-3

- LAG-3 is expressed on activated T cells, regulatory T cells, γδ T cells, NK cells, and pDC

Goldberg, M. et al 2011
Overview

- Overview of TIM-3 and LAG-3
- Expression on immune cells in the tumor microenvironment
- Function in limiting anti-tumor immune response
- Expression of TIM-3 and LAG-3 following PD-1 blockade
- Do you always need PD-1 blockade?
TIM-3 and LAG-3 Expression and Association with PD-1 in Patients with NSCLC

Advanced stage NSCLC correlates with increased TIM-3 and LAG-3 expression on PD-1^{hi} cells

**TIM-3**

![Graph showing TIM-3 expression across different stages of NSCLC]

**LAG-3**

![Graph showing LAG-3 expression across different stages of NSCLC]
TIM-3 co-expression is greatest on PD-1$^+$ cells followed by CTLA-4$^+$ and LAG-3$^+$ with minimal co-expression with BTLA.
Regulatory T cell Expression of Immune Checkpoints in Tumors Correlates with Increased Suppression

Tregs expressing CTLA-4, TIM-3, and PD-1 are enriched in tumors and this correlates with increased suppressive activity.

Jie, H-B et al. BJC 2013
Overview

- Overview of TIM-3 and LAG-3
- Expression on immune cells in the tumor microenvironment
- Function in limiting anti-tumor immune response
- Expression of TIM-3 and LAG-3 following PD-1 blockade
- Do you always need PD-1 blockade?
TIM-3 Blockade Improves Control of Tumor Growth in Pre-Clinical Models

Blockade with TIM-3 or PD-1 alone has moderate activity in multiple tumor models while combination improves tumor control.

Sakuishi et al. 2010; Ngiow et al., 2011
TIM-3+PD-1+ CD8+ T cells produced lower levels of TNFα and IFNγ than their Tim-3neg counterparts.

Blockade of TIM-3 and PD-1 results in improved cytokine secretion.
Overview

- Overview of TIM-3 and LAG-3
- Expression on immune cells in the tumor microenvironment
- Function in limiting anti-tumor immune response
- Expression of TIM-3 and LAG-3 following PD-1 blockade
- Do you always need PD-1 blockade?
Tim-3 Expression as a Compensatory Mechanism of Immune Suppression Following PD-1 Blockade

Development of resistance to PD-1 blockade in two GEMM models is associated with increase in TIM-3 expression on T cells

CD8 TIL from SCCHN tumors exposed to anti-PD-1 ex vivo results in increased expression of TIM-3 (Shayan, G. et al. SITC 2015)
Overview

- Overview of TIM-3 and LAG-3
- Expression on immune cells in the tumor microenvironment
- Function in limiting anti-tumor immune response
- Expression of TIM-3 and LAG-3 following PD-1 blockade
- Do you always need PD-1 blockade?
Do you always need PD-1 blockade?

Ipilimumab and IL-2: ~15% durable responses in the absence of PD-1 blockade
The Balance of Immune Cell Activation

Inhibition of multiple inhibitory receptors enhances T cell-mediated anti-tumor immune responses

Compensatory up-regulation of immune inhibitory receptors following blockade of one axis

Opportunity to impact multiple aspects of the anti-tumor immune response due to expression of TIM-3 and LAG-3 on multiple immune cells
Acknowledgements

- **Tesaro**
  - Yonghang Xiao
  - Dmitri Bobilev
  - Haley Laken
  - Keith Wilcoxen
  - Immuno-Oncology Team

- **AnaptysBio**