Tim-3 as a target for tumor immunotherapy

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Disclosures

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Outline

• Immune checkpoint molecules:
  • Tim-3 vs PD-1

• Role of Tim-3 and PD-1 in anti-tumor immunity:
  - T cell exhaustion
  - Regulatory T cells
Immune checkpoint molecules

• Definition- negative regulatory molecules upregulated on activated T cells that serve to contract ongoing T cell responses thereby preventing uncontrolled immune responses and ensuing immunopathology

• CTLA-4, PD-1, Tim-3, Lag-3

• Cancer - Dysregulated expression of immune checkpoint molecules on T cells

• Clinical relevance: immunotherapies that target immune checkpoint molecules have been shown to improve immunity in cancer (mice and human)
T cell exhaustion

• Exhaustion - state of T cell dysfunction - failure to proliferate and exert effector function in response to TCR stimulation

• Hierarchy of exhaustion - loss of proliferation/CTL function and IL-2, then loss of TNF$_\alpha$, then loss of IFN$_\gamma$

• Express PD-1 and blockade of PD-1/PD-L1 interactions partially restores T cell function

• Exhausted T cells also express Tim-3 (HIV, HCV) and blockade of Tim-3 signaling restores T cell function
Tim-3 vs PD-1

Expression:
• PD-1 is upregulated on all T cells 24-72 hrs after activation
• Tim-3 is selectively expressed on IFN-γ-secreting CD4+ and CD8+ T cells

Signaling:
• PD-1 has ITIM and ITSM motifs in cytoplasmic tail
• Tim-3- 6 tyrosine residues in cytoplasmic tail- no ITIM or ITSM

Ligands:
• For PD-1: PD-L1 (widely expressed) and PD-L2
• For Tim-3: galectin-9- widely expressed

• Both Tim-3 and PD-1 ligands are upregulated by IFNs and expressed on tumors
Expression of Tim-3/PD-1 and their ligands on tumor cell lines

CT26

B16F10
High frequency of Tim-3⁺ PD-1⁺ cells in CD8 positive Tumor Infiltrating Lymphocytes (TILs)

One-Way ANOVA,
Tukey’s multiple comparison test
*p<0.001, **p<0.05
LAG3 and CTLA-4 expression on Tim-3 and PD-1 expressing TILs

CD8 TILs

A

Tim-3⁻ PD-1⁻  Tim-3⁻ PD-1⁺  Tim-3⁺ PD-1⁺

B

Tim-3⁻ PD-1⁻  Tim-3⁻ PD-1⁺  Tim-3⁺ PD-1⁺

LAG3

CTLA4
Tim-3⁺PD-1⁺ CD8 TILS are more impaired in cytokine production relative to Tim-3⁻PD-1⁻TILS.
Tim-3 and PD-1 expression in cytokine non-producing TILS

*\(p<0.0001\)
Tim-3 and PD-1 expression in CD8⁺TILS entering cell cycle

P<0.05, One-Way ANOVA, Tukey’s Multiple Comparison Test
Effect of targeting the Tim-3 and PD-1 signaling pathways on CT-26 tumor growth

![Graph showing the effect of targeting the Tim-3 and PD-1 signaling pathways on CT-26 tumor growth.](image-url)
Combined targeting of Tim-3 and PDL-1 in melanoma
Anti-Tim-3 and Anti-P-L1 Antibody Treatment of established Tumors

CT26

- Control
- Anti-Tim-3 Ab + Anti-PDL-1 Ab

2/5 complete regression

Anti-Tim3 Ab
Anti-PD-L1 Ab
Tim-3 and PD-1 marks exhausted cells in AML

Zhou et al. Blood 2011
Combined therapy increases survival in AML

Zhou et al. Blood 2011
Why target both Tim-3 and PD-1?

Pre-clinical models of cancer

• Tim-3 and PD-1 are uniquely co-expressed in TILs
  • CD4 FoxP3+ Tregs
  • CD8 exhausted phenotype
• In both solid and non-solid cancers combined targeting of the Tim-3 and PD-1 pathways is a highly effective therapy

• Human cancer (melanoma mets)
  • CD8+ TILN vs PBL: exhausted phenotype only in TILN,
    Expression of inhibitory receptors (Tim-3, PD-1) enriched in TILN (Baitsch et al JCI 2011)
  • Blockade of Tim-3 and PD-1 (in vitro) synergizes to increase cytokine production in melanoma specific T cells (Fourcade et al JEM 2010)
Additional reasons to target Tim-3 in cancer

• Tim-3 has a role in promotion of myeloid-derived suppressor cells (MDSC) \((Dardalhon et al, JI 2010)\)

• Tim-3 is expressed on cancer stem cells- AML (human)
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