POSTER PRESENTATION

Open Access

TIM-3⁺ T cells are not exhausted but activated cells in the tumor microenvironment

Hyun-Bae Jie^{1*}, Jing Li¹, Raghvendra Srivastava¹, Robert L Ferris^{1,2,3}

From Society for Immunotherapy of Cancer 28th Annual Meeting
National Harbor, MD, USA. 8-10 November 2013

Although T-cell immunoglobulin mucin 3 (TIM-3) does not contain inhibitory or death signaling motifs in its cytoplasmic domain, it has been proposed to be associated with T cell suppression and/or exhaustion. However, several lines of evidence suggest that TIM-3 can stimulate T cells as a costimulatory molecule by coupling Src family tyrosine kinase Fyn and the p85 phosphatidylinositol 3-kinase (PI3K) adaptor to TCR signaling. We examined the expression pattern and function of TIM-3 and other immune checkpoint receptors, CTLA-4 and PD-1 on tumor infiltrating lymphocytes (TIL), compared to those of peripheral blood T lymphocytes (PBL) in patients with head and neck cancer (HNC). Here, we report that TIM-3⁺CD8⁺ TIL express higher granzyme B/perforin, more actively proliferate under anti-CD3/-CD28 stimulatory conditions, and are more resistant to activation induced cell death than TIM-3⁻CD8⁺ TIL, indicating TIM-3 can positively regulate T cell responses. Analysis of downstream signaling molecules including phosphorylated JAK/STAT-1, PD-1/SHP-2, and costimulatory CD137 in CD8⁺ TIL subsets supports our observation that TIM-3⁺CD8⁺ TIL are activated cells in HNC patients. However, PD-1 and CTLA-4 can negatively regulate immune responses of TIM-3⁺CD8⁺ and TIM-3⁺CD4⁺ TIL respectively. More importantly, neoadjuvant immunotherapy of HNC patients with the EGFR-specific mAb cetuximab increased both TIM-3 and PD-1 expression on CD8⁺ TIL, which was correlated with higher granzyme B/perforin expression in TIM-3⁺CD8⁺ TIL. Taken together, these findings suggest that TIM-3 functions as a positive regulator of activated T cells in the tumor microenvironment while CTLA-4 and PD-1 modulate the function of activated TIM-3⁺ TIL. We therefore suggest that TIM-3 can be used as a biomarker to indicate activation status of T cells in the tumor microenvironment depending on PD-1

co-expression, particularly in response to cancer therapy including cetuximab-based immunotherapy.

Authors' details

¹Otolaryngology, University of Pittsburgh, Pittsburgh, PA, USA. ²Immunology, University of Pittsburgh, Pittsburgh, PA, USA. ³Cancer Immunology Program, University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA.

Published: 7 November 2013

doi:10.1186/2051-1426-1-S1-P190

Cite this article as: Jie et al.: TIM-3⁺ T cells are not exhausted but activated cells in the tumor microenvironment. *Journal for ImmunoTherapy of Cancer* 2013 **1**(Suppl 1):P190.

**Submit your next manuscript to BioMed Central
and take full advantage of:**

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at
www.biomedcentral.com/submit

¹Otolaryngology, University of Pittsburgh, Pittsburgh, PA, USA
Full list of author information is available at the end of the article